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NO MARCH NUMBER.

This number of the Archives of Internal Medicine—which should be the March number—has been unavoidably delayed. The Postoffice rulings require that it bear the date of the month of issue, which will explain why this appears as the April number. While there will be no March number, each volume will consist of six numbers as announced.

ROLE OF VENOUS CONGESTION IN COMPENSATION OF TRICUSPID INSUFFICIENCY.

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The possibility of the establishment of compensation in the lesions of the tricuspid valve was doubted by Romberg (Cf. Franke[2]) and hesitatingly admitted by Krehl (Cf. Franke[2]) on account of the weakness of the right auricle, which is the only cavity of the heart left to perform the task. MacKenzie[1] and others have, however, described cases of tricuspid insufficiency lasting over long periods. Recently, Franke[2] has cited several cases where, in the light of the literature, he believes that dilatation and hypertrophy of the right auricle and ventricle, venous congestion, and especially congestion of the liver were factors in maintaining compensation.

The clearness with which the rôle of venous congestion as an element in compensation is demonstrated makes the following case worthy of record:

History.—The patient, an adult white female with a long-standing heart lesion, developed ascites. There was mitral insufficiency, secondary tricuspid insufficiency, and enlargement of the heart which extended beyond the anterior axillary line. The usual murmurs were present. The jugulars were greatly distended. Shortness of breath had been pronounced for many months. Edema of the lower extremities, varying in extent, had been present for a long time. There had been periods of broken compensation.

With the onset of swelling of the abdomen, these signs were not materially changed. The patient had not been seen for a number of weeks when, on account of urgent dyspnea and rapid action of the heart, the physician was called.

Examination.—The heart was slightly displaced upward. The action was so tumultuous that, on auscultation, nothing could be determined with certainty. No radial pulse could be found. The jugulars were collapsed in diastole, and in systole presented a very large wave. The face was pale and the lips showed but a little color. There were no signs of congestion about the face, neck or upper extremities. Dyspnea was distressing. The abdomen was greatly distended and tense, the subcutaneous edema extensive. The lower extremities were greatly swollen and shapeless.

Treatment.—The abdomen was tapped and immediately after the pressure was reduced the following conditions were noted: The rate of the heart's action became regular and slower; the radial pulse returned. On auscultation, half an hour later, the murmurs had returned. The jugulars were greatly distended and the systolic pulsation reduced in extent. The face was at first congested, with the

1. Am. Jour. Med. Sc., 1907, cxxxiv, 12.
2. Wien. klin. Wchnschr., 1906, xix, 956.

lips blue. Within a few minutes, however, the lips became red and the respirations were slower, deeper and easier. After the first reaction the patient became more comfortable.

The points of especial interest in this case appear to be the following:

1. (a) The congestion of the superior cava, caused by the cardiac lesion, continued until the abdominal pressure obstructed the inferior cava, after which the branches of the superior cava were freely drained by the heart. (b) The congestion of the superior cava reappeared as the obstruction of the inferior cava was removed by reducing the abdominal pressure. (c) The diminution of the congestion of the superior cava was followed by a large systolic venous pulsation which diminished in extent as the congestion returned.

2. The heart's action was phenomenally tumultuous and the quantity of blood delivered to the arteries was very small; there was no palpable radial pulse.

3. Withdrawal of fluid from the abdomen was followed by congestion of the veins and lips, a retardation of the heart's action, a very great improvement in the character of the radial pulse, and a relief of the dyspnea.

4. The previous history pointed to the existence of tricuspid insufficiency.

Physiologic data show that the capillary pressure may vary from zero to 50 mm. of mercury, ranging under normal conditions from 10 to 30 mm. If a ligature be placed about a finger, the capillary equals the static arterial pressure. It is, moreover, fallacious to argue that a fall of arterial pressure necessarily produces a fall of pressure in all of the capillary areas of the body.[3] The capillary pressure is normally from one-sixth to one-third of the arterial pressure.

The venous pressure is also influenced by the arterial pressure. Schäfer[4] says: "When all the venous exits from any part are ligated, then the pressure rises, peripherally to the seat of ligation, to the arterial pressure."

If the pressure in an obstructed vein from any part may rise to the arterial pressure, the same principle should apply to the entire venous system. This has been shown to be true by Cohnheim's[5] experiments on pericardial pressures. Cohnheim inserted canulæ in the pericardium, femoral artery and jugular vein. Oil was injected into the pericardium and pressures were measured in millimeters of oil for the pericardium,

3. Schäfer, Text-Book of Physiology, ii, 116.
4. Vol. i, p. 121.
5. Allgemeine Pathologie, 1882, Bd. 1, 22.

in millimeters of mercury for the femoral artery, and in millimeters of soda solution for the jugular vein. The results were as follows:

1. Thirty mm. of oil pressure was taken up by the elasticity of the pericardium without change of pressure in either the femoral artery or jugular vein.

2. Sixty to 70 mm. of oil pressure caused a drop of 20 to 30 mm. of mercury in the femoral artery and a rise of 60 mm. of soda solution in the jugular vein.

3. One hundred to 120 mm. of oil pressure produced a fall in the femoral pressure to half its original height and a rise to 100 mm. of soda solution in the jugular vein.

4. Two hundred and forty to 320 mm. of oil pressure caused a cessation of pulsation in the pulmonary artery, but the femoral continued to pulsate and registered a pressure of from 10 to 15 mm. of mercury; the venous pressure was 220 to 240 mm. of soda solution.

On removing the pericardial pressure the circulation returned to its original condition, save for a few minutes when the arterial pressure was above its original point. If in (4) the femoral pressure is converted into terms of soda solution, 133 to 200 mm., it is apparent that the venous pressure equals the arterial when the flow from the veins is blocked and the system becomes a closed pipe. In other words, the circulation in the systemic arteries, capillaries and veins is really one and is controlled by the same principles as those governing the action of fluids in an open or closed system of pipes.

In a closed system the pressure is the same throughout, as illustrated in Cohnheim's experiment when the venæ cavæ were blocked, as in (4). Here the pressure in the cavæ and arteries was equal. In a partially closed system the pressure in the end distal to the pressure head is equal to that of the pressure head minus friction and flow. In Cohnheim's experiment the venæ cavæ were partially closed as in (3). The decreased flow of blood caused the arterial pressure to fall and the venous pressure to rise. The system being partially closed, the pressure throughout was proportionately equalized. In the normal condition the open ends of the system, the venæ cavæ, register zero or less. Here all of the pressure head is consumed in friction and flow.

The storage of blood in the veins is due to the arterial flow, and the pressure under which the blood is maintained in the veins is the arterial pressure minus friction and flow. The venous congestion may be compared to a closed system in which, while the blood is stationary, the pressure represents potential energy; while flowing, kinetic energy. During life, venous congestion is associated with and to a degree equal to the

active force obstructing the flow of blood in the vein. It represents the potential energy of the arterial pressure or left ventricle, transferred from source of power of a partially closed tubular system to the distal end, to be used, as kinetic energy, in overcoming or compensating the force obstructing the flow of blood in the vein. The left ventricle compensates venous obstruction.

Supported as it is, this theory as to the nature of venous congestion should form a safe basis for a consideration of some of the mechanics of pathologic circulatory changes. It is generally acknowledged that mitral insufficiency is usually associated with hypertrophy and dilatation of the left auricle and ventricle, pulmonary congestion and varying degrees of hypertrophy of the right ventricle (compare Mority[6]). In tricuspid insufficiency, hypertrophy and dilatation of the right auricle and ventricle may be compared with the similar changes in the left heart in mitral insufficiency; while the general venous congestion may be regarded as analogous to the pulmonic congestion. The rôle of the right ventricle in mitral lesions has, however, no counterpart in disease of the tricuspid valve. Both Stadler[7] and Franke[2] assert that, because of atrophy, it is impossible for the left ventricle to play a part in the compensation of tricuspid insufficiency.

In the case cited, the course of events was probably somewhat as follows: There was hypertrophy and dilatation of the heart, tricuspid insufficiency and intense venous congestion. The development of a terminal ascites gradually obstructed the inferior cava. As this obstruction developed, the flow of blood to the heart diminished until the superior cava and its branches were relieved of their former congestion, thereby removing all traces of congestion from the head and upper extremities. The jugular vein was collapsed in diastole, and in systole a large pulsation, due to backflow from the right ventricle, was present. The presence of the backflow into the superior cava which was not congested shows that, when the tricuspid lesion had developed, the backflow takes no part in the causation of congestion.

In this case the superior cava was an open system in which the pressure at the extremity distal to the power should be low; while the power was much reduced, thereby diminishing the amount of blood which could, under low pressure, be forced through the capillaries. The low arterial pressure was indicated by the absence of radial pulse. The right ventricle was competent to move forward all the blood delivered by the venæ cavæ, as was shown by the condition of the superior cava. This

6. Deutsch. Arch. f. klin. Med., 1899, lxvi, 421.
7. Deutsch. Arch. f. klin. Med., 1905, lxxxiii, 71.

competency of the right ventricle was due to rapid and forcible action of the heart. The low pressure in the superior cava developed when the amount of blood delivered to the systemic veins was less than that delivered to the pulmonic artery. The inferior cava, obstructed by the peritoneal pressure, was congested by a pressure which, undoubtedly, was equal to the low arterial pressure; and the circulation in the lower portion of the body was almost *nil,* as indicated by the extreme edema.

The absence of congestion of the superior cava, its presence in the inferior cava as a result of ascites, and the existence of the backflow which had no appreciable effect on the circulation in the superior cava, suggest that, in tricuspid insufficiency, the activity of the right ventricle may be considered under two heads: 1. The effort expended in pumping blood into the pulmonic artery. This factor is deficient as compared with the normal and is the immediate cause of venous congestion. 2. The effort expended in propelling the regurgitant blood into the auricle and veins. The production of this backflow acts mechanically by increasing, first, the auricular and, later, the auricular and venous pressure so as to build, at the tricuspid opening, a wall, so to speak, of blood under high pressure, which, in part, takes the place of the tricuspid valve. This may be regarded as a utilization of a portion of the congested blood.

The large systolic venous pulsations, the absence of radial pulse and the forcible rapid heart action show that only a small amount of blood was delivered to the arterial system and that a large portion of the blood was returned during each systole to the veins and right auricle in which the pressure was low. Hypertrophy and dilatation of the right ventricle and, as MacKenzie[1] suggests, the right auricle, were the only active compensatory factors. They were unequal to the task, leaving the heart to exhaust itself by rapid action which moved a minimum amount of blood and delivered a minimum amount of nutrition to the heart.

When the abdominal pressure was relieved, congestion in the venæ cavæ and distention of the right auricle were immediately re-established, thus furnishing a pressure of a degree sufficient to diminish the tricuspid regurgitation and to raise the pressure in the right ventricle to such an extent that a larger amount of blood was delivered to the pulmonic circulation and left heart. The dyspnea was then diminished; the heart's action was reduced in rate and regular, the radial pulse returned, and the large systolic venous pulsation was diminished in size.

It should be noted that, after the abdominal pressure was removed, the right ventricle had sufficient strength to perform the required work; it must consequently be inferred that the ventricle had the power necessary to pump the usual amount of blood while the inferior cava was ob-

structed. But during this period the low pressure in the auricle and superior cava offered the path of least resistance for the greater portion of the small amount of blood delivered by the superior cava. Venous congestion is the resistance on which the hypertrophied right ventricle must depend for support.

The right ventricle would thus appear to depend on venous congestion of a degree sufficient to maintain a pressure which, with the addition of that contributed by the backflow, may offer resistance enough to act as a substitute for the insufficient tricuspid valve. Now, since the venous congestion depends on, is caused by and represents the arterial pressure, minus friction and flow, or, in other words, the activity of the left ventricle, it follows that in tricuspid insufficiency the left ventricle bears the brunt of that part of compensation which is played by venous congestion.

As the flow of blood to the left heart is diminished, the work of the left ventricle is progressively lessened. The left ventricle may, therefore, remain of normal thickness or it may become atrophied. The large normal excess of arterial pressure over that in the capillaries renders it possible that even with diminished activity of the left ventricle and a lowered arterial pressure there may yet be a rise in venous pressure, a portion of which is utilized for compensation, the balance being consumed through friction and flow of blood.

The factors in tricuspid compensation usually considered[8] are: 1. Hypertrophy and dilatation of the right auricle. 2. Venous congestion. 3. Hypertrophy and dilatation of the right ventricle. 4. Aspirating effect of the thorax with inspiration.

1. As the tricuspid valve begins to leak, the right auricle is distended and hypertrophies to some extent. But when the lesion becomes extensive, as in this case, the auricle plays a minor rôle, if, indeed, it plays an active part at all; it is, however, probably inactive, as shown in one case by Franke,[2] and especially noted by MacKenzie.[1] If inactive, it virtually becomes a portion of the venous system.

2. The venous congestion, compensatory venous congestion, may be considered under two heads: (a) the constant or accumulated (diastolic) pressure from the arterial system, and (b) the pressure added by the backflow from the right ventricle.

These pressures serve two purposes: First, the constant pressure maintains the venous distention, so that, with the backflow of blood under a relatively high pressure, the venous pressure rapidly rises to a

8. Sahli: Diagnostic Methods. Transl. by Kinnicutt and Potter from fourth German edition, 1905, 335.

maximum, after which the greatest possible amount of blood enters the pulmonary artery. Second, the maximum venous pressure aids in filling the ventricle during diastole. Through its elasticity, experimentally shown by Salamon,[9] the liver in the pulsating venous system serves the same purpose as an air chamber in a force pump; it also supplies storage for blood.

3. Hypertrophy of the right ventricle is required to develop the added systolic venous pressure and to perform the extra amount of work due to the size of the ventricular cavity when there is dilatation. Here, to propel the usual amount of blood, the muscle or power moves over a shorter distance, consequently must do more work. A certain amount of dilatation is necessary for compensation, supplying space for the blood which is returned in systole to the auricle and veins. Dilatation beyond this point furnishes storage room for blood.

4. Aspiration with inspiration is a minor factor.

5. To this test should be added the work of the left ventricle which is represented by the venous congestion.

Of these factors, the venous congestion and the hypertrophy and dilatation of the right ventricle are the most important. Impairment of either factor leads to heart failure, each in its own way.

In the one event the heart, deprived of the venous pressure against which it works, exhausts itself by increased activity and an ever-diminishing amount of nutrition until it can no longer contract. At autopsy the heart and cavæ should contain little blood. In the other event, if the right ventricle fail, the right heart and veins are so distended with blood that the weakened heart muscle is unable to contract. At autopsy the right heart and veins are distended with blood, while the left heart contains little or no blood.

CONCLUSIONS.

In tricuspid insufficiency the left ventricle and venous congestion play the same rôle as do the right ventricle and the pulmonary congestion in mitral insufficiency. In the latter condition the congestion of the auricle and the pulmonary circulation furnishes the resistance against which the hypertrophied left ventricle works; in the former the congestion of the right auricle and cavæ favor the action of the hypertrophied right ventricle.

In the one, the right ventricle causes the pulmonic congestion; in the other, the left ventricle, the caval congestion. This is as it should be, for in each circulation the ventricle is best fitted to develop the neces-

9. Salamon: Lancet, London, 1907, I, 4.

sary venous pressure. The remaining factors have a temporary or minor influence on the compensation of insufficient mitral and tricuspid valves.

SUMMARY.

Mitral Insufficiency.

L. auricle. { Dilatation. / Hypertrophy.

L. ventricle. { Dilatation. / Hypertrophy.

Pulmonic veins, congestion.
Pulmonic artery, congestion.
R. ventricle, hypertrophy.
Increased resistance.

Tricuspid Insufficiency.

R. auricle. { Dilatation. / Hypertrophy.

R. ventricle. { Dilatation. / Hypertrophy.

Systemic veins, congestion.
Systemic arteries, low pressure.
L. ventricle, normal or atrophied.

The normal margin of arterial pressure above that in the capillaries makes possible a decrease in the arterial pressure (l. ventricle either normal or atrophied) in the presence of a rise in the capillary pressure, until the venous, capillary and arterial pressures are relatively the same, or until the flow of blood through the capillaries is insufficient to sustain life.

TUBERCULOUS ULCER OF THE STOMACH, WITH REPORT OF A CASE.*

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AND
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According to Boas, three forms of tuberculosis of the stomach may be distinguished: the tuberculous granulomata (the rarest form), miliary tuberculosis of the gastric mucous membrane (the most frequent form), and finally tuberculous ulcer of the stomach.

The comparative rarity of tuberculous ulcer of the stomach may be gathered from the following facts: Hamilton,[1] in a careful study of the reported cases, was able to collect but 15 positive and 9 doubtful. Blumer[2] collected but 30 reliable instances. Arloing,[3] in his classic thesis, gives 147, but he was not so discriminating as the writers mentioned above and included a number which they had rejected. In view of the generally accepted fact that tuberculosis of the stomach is practically always secondary to a tuberculous process elsewhere, the autopsy records on tuberculous patients is of value here:

Simmonds	8 cases in	2,000 autopsies.
Steiner and Neureutter	4 cases in	302 autopsies.
Widerhofer	2 cases in	418 autopsies.
Soltau Fenwick	2 cases in	2,000 autopsies.
Papavoine	1 case in	50 autopsies.
Villegk	5 cases in	1,317 autopsies.
Barthez and Rilliet	6 cases in	141 autopsies.
Müller and Hecker	8 cases in	297 autopsies.
Gerhardt	2 cases in	418 autopsies.
Still	5 cases in	226 autopsies.
	43 cases in	7,169 autopsies = 0.7

It would appear from Arloing's collected figures that tuberculosis of the stomach is more common in general miliary tuberculosis than in the chronic forms; thus Simmonds, among 100 cases of general miliary tuberculosis, found one instance where the stomach had been attacked. Frerichs noted 3 among 30 cases of miliary tuberculosis and only 7 in 250 of the chronic form.

* Read before the Medical Society of the District of Columbia, February, 1908.

1. Bull. Johns Hopkins Hosp., April, 1897, p. 75.
2. Albany Med. Ann., 1898, p. 145.
3. Thesis, Lyons, 1902-3.

As to whether tuberculous lesions of the stomach are more common in children or in adults, we may again borrow from Arloing. His collected figures show that in 2,115 autopsies on tuberculous children there were 38 instances of stomach involvement (1.7 per cent.), while in 4,917 autopsies on tuberculous adults there were but 23, or 0.45 per cent. In spite of these figures, this author is of the opinion that the condition is more often seen in adults.

As to the favorite location of the ulcers there is some difference of opinion. Ricard and Chevrier,[4] from their collection of statistics, found that the pyloric region extending one or two centimeters from the opening was involved in about 35 per cent. of the cases; then the greater curvature, 20 per cent.; then the posterior surface, the lesser curvature, the anterior surface, and the subcardiac region. Tripier would place the lesser curvature immediately after the pylorus in frequency of involvement. The apparent preference for the pyloric end of the stomach has been explained by Virchow and Rokitansky as due to the more numerous lymphatic follicles in this locality.

HISTORIC DATA.

The first mention of tuberculous ulcer of the stomach is said to have been made by Andral and Cruveilhier in their treatise on pathologic anatomy in 1842. Since that time brief reference has been made by various authors of text-books to this condition. Bignon in 1853 published the first detailed account of a case of tuberculous ulcer of the stomach. Litten and Talamon in 1879 reported cases in which giant cells were found in microscopic examination of sections from ulcers. Coats[5] in 1886 inaugurated a new era by demonstrating the specific bacilli in the lesions. Musser's[6] case, the report of which appeared in 1890, was the first published in America in which Koch's bacilli were found.

In looking up cases recorded as tuberculous ulcers of the stomach, one is confronted with the difficulty of determining their authenticity. At the risk of excluding some in which there is little doubt as to the genuineness, it would seem best to accept only those in which a microscopic examination shows either a typical tuberculous picture or the tubercle bacilli in the walls of the ulcer. This careful scrutiny seems the more necessary when we realize that the generally anemic and depraved physical condition of tuberculous patients renders them exceptionally good subjects for simple ulcer of the stomach. It is very likely

4. Rev. de chir., 1905, xxxi, pp. 74 and 557.
5. Glasgow Med. Jour., 1886, xxvi, p. 53.
6. Phila. Hosp. Rep., 1890, i, p. 117.

that not a few phthisical patients suffer from peptic ulcers and the finding of the bacilli on the surface of such ulcers is no proof of their being truly tuberculous, as shown by Blumer and Happel's[7] case of pulmonary tuberculosis associated with round ulcer of the stomach.

MODE OF INFECTION.

There are four avenues by which tuberculous infection might reach the stomach, viz.: by direct infection of the mucous membrane, through the lymphatics, through the blood stream, and through the serous coat.

The first-mentioned mode of infection might appeal to us strongly because of the apparent ease with which the bacillus might be brought in contact with the mucous membrane of the stomach by the swallowing of infected sputum by those whose lungs are tubercular, and in infected food, but the best authorities do not consider this the usual manner. Arloing,[3] in his experiments on dogs, was unable in a single instance to produce ulcer of the stomach by administration of infected materials, his experiments including mechanical irritation and devitalization of areas of the mucosa by ligation of vessels and alterations in the chemical reactions of the gastric juice.

Through the lymphatic system the bacilli might gain entrance directly into the lymphatics of the stomach, or through the contiguity of an infected lymphatic gland; thus a tuberculous gland may become adherent to the wall of the stomach and ulcerate through. In our case there were three large caseous glands behind the ulcer, one of which was closely adherent to the floor of the ulcer and showed microscopic communication with it.

Infection through the blood stream is believed by Arloing to be the most usual method. To support this theory, he brings the fact that in his numerous experiments on animals he was but twice able to produce a tuberculous gastric ulcer, and in both of these cases the bacilli had been injected into the blood stream. In one there had also been an intraparietal injection. One of these artificially produced ulcers was situated in the duodenum, but to all intents and purposes a duodenal ulcer is practically the same as a gastric ulcer. The fact that tuberculous gastric ulcers are more common in acute miliary tuberculosis also strengthens this theory. Infection through the serous coat of the stomach is admitted as at least possible, although certainly very unusual.

We wish here to report a case of large single tuberculous ulcer of the cardiac end of the stomach without pulmonary involvement.

7. Albany Med. Ann., 1898, p. 594.

Patient.—M. J., aged 18, female, single, was admitted to the Garfield Memorial Hospital April 12, 1907.

Family History.—Negative.

Previous History.—Diseases of childhood; otherwise healthy.

Present Illness.—The patient has not been well for the past few months, but is unable to state exactly when illness began. Appetite has been poor. Has lost weight greatly. Was treated in Freedman's Hospital for three weeks about three months ago (does not remember exact date), and at that time she had persistent vomiting which occurred a few minutes after taking food or water and was not accompanied by nausea. There was diarrhea. Vomitus and dejecta sometimes contained blood (?). Now she complains of pain in throat, particularly on swallowing. There is vomiting and diarrhea, but not so severe as formerly. There is no cough but she raises considerable mucus from throat. She complains of a swelling in the upper part of the abdomen. Owing to the patient's low grade of mentality and weakened physical condition, the history was obtained with difficulty and is unsatisfactory.

Physical Examination.—Emaciation extreme. Slight exophthalmos. Tongue clean, smooth and red. Pulse small, regular and frequent. Heart normal. Lungs normal. There is a distinct protrusion in the epigastric region, the most prominent point of which is in the median line, one-third of the distance from the xiphoid to the umbilicus. The abdominal wall is extremely tense, especially over the above-mentioned area. There is marked tenderness on pressure over the tumor, which is smooth and conforms in its general outline to an enlarged liver (which it later proved to be). The lower border of the right lobe of the liver is found to be on a level with the umbilicus; the lower border of the left lobe about two inches higher. Liver dulness begins above in the nipple line at the fifth interspace and extends downward to a horizontal line just above the umbilicus. The left lobe extends to a point about two inches higher. There is dulness over the lower portion of Traube's semilunar area. Posteriorly the liver dulness extends below its normal position. The spleen can not be distinctly outlined. There are no superficial glandular enlargements. Knee jerks are absent. The record of the pulse, respirations and temperature were of no value from a diagnostic point of view. There was vomiting and diarrhea with involuntary movements. The various examinations in the clinical laboratory threw but little light on the case. These were as follows:

SPUTUM: April 14.—Negative to tubercle bacilli.

VOMITUS: Very sour fluid with strong acid reaction. Contains milk curds and a large amount of mucous of a purulent character. Trace of lactic acid. Microscopic examination showed numerous leucocytes, no red cells, numerous large bacilli, sarcinæ and other organisms.

BLOOD: April 6.—

Hemoglobin	80 per cent.
Red cells	4,848,000
Leucocytes	15,200

April 15.—

Hemoglobin	70 per cent.
Red cells	4,920,000
Leucocytes	28,200

Differential leucocyte count, 500 cells:

Small lymphocytes	16.0
Large lymphocytes	2.8
Transitional	1.0
Polynuclear	80.0
Eosinophile	.2
	100.0

URINE: April 6.—Acid reaction. Specific gravity, 1015. Albumin, 7 per cent. Granular casts. Numerous leucocytes.

April 13.—Acid reaction. Specific gravity, 1007. Albumin, 5 per cent. Hyaline and granular casts. Numerous leucocytes.

April 17.—Acid reaction. Specific gravity, 1015. Albumin, 8 per cent. Granular casts. Numerous leucocytes.

FECES: April 15.—Light yellow fluid stool, with granular sediment. Offensive odor. Few epithelial cells and leucocytes. No red cells. Cercomonos intestinalis numerous.

Treatment and Result.—From the history and from the enlarged liver, malignant disease of the stomach, with probably a secondary involvement of the former organ, was suspected in spite of the patient's age (18 years). With the possibility of tuberculous peritonitis in view, Dr. A. A. Snyder opened the abdomen and discovered very minute miliary tubercles on the small intestine, though no active inflammatory condition existed. Death occurred shortly afterward. The extreme tenderness over the liver, especially in the epigastric region, already mentioned, must have been due to the large gastric ulcer disclosed at the autopsy, the details of which follow. Tuberculous ulcer of the stomach was not suspected, though the history suggested a possible ulcer.

AUTOPSY—MACROSCOPIC EXAMINATION.

General Appearance.—Small negro girl. Much emaciated. Bones small and symmetrical. Marked depression of supraclavicular and infraclavicular regions, not so marked in intercostal spaces. Breasts relatively well developed. No skin lesions.

Respiratory System.—Larynx normal. Lungs collapsed on opening thoracic cavity. They are of a pinkish-white color and mottled with anthracotic pigment, soft, crepitant and float in water. On section, moderately moist, reddish-pink color and pigmented. Bronchi contain pinkish frothy material. Neither lung shows any adhesions. The pleura is a light pink color and smooth throughout; no adhesions. Bronchial glands not enlarged and show no gross evidence of tuberculosis.

Circulatory System.—Heart small, weighing 145 grams. Normal position. Brownish-red color and flabby texture. Aortic and pulmonary valves normal. The tricuspid leaflets thickened and show areas of opacity. Anterior leaflet of mitral valve thickened, yellowish white and quite hard. All cavities contain dark clotted blood. Pericardium normal. No atheroma of aorta.

Lymph Glands.—The retroperitoneal glands were much enlarged, forming a fusiform tumor along the left of the spinal column for about six inches, the upper pole lying beneath the left lobe of the liver. These glands are conglomerate, soft, of a greenish-yellow color, and completely necrotic from cheesy degeneration. The centers of some of them have undergone liquefaction. The glands along the lesser curvature of the stomach, portal vein, behind the stomach, and around the head of the pancreas are also enlarged and similarly affected. The mesenteric glands are but slightly enlarged and are congested. Near the intestinal ulcer is one the size of a pea. Superficial glands are not enlarged.

Spleen.—Bright red color, dry, firm and greasy on section. Usual markings replaced by lobular like structure. Weight, 130 grams. Iodin reaction for amyloid.

Thyroid Gland.—Normal.

Liver.—Ten cm. below costal arch in midaxillary line; 12 cm. below ensiform. On left extends to junction of midclavicular line and ninth costal cartilage. Upper relations normal. Weight, 1,800 grams. Firm and slightly nodular to the touch. Reddish green color. On section, dry, firm and greasy. Iodin reaction for amyloid

positive. The nodules beneath the capsule are small, yellowish white and soft, and similar areas are seen deeper in the organ.

Pancreas.—Normal in size and situation. Head firmly bound down by adhesions with enlarged glands. On section head shows areas of cheesy degeneration. None found in tail.

Kidneys.—Normal position. Pale, firm and greasy. Weight of right, 140 grams; left, 160 grams.

Genital Organs.—Uterus small and retroflexed by adhesions. Right ovary prolapsed into cul-de-sac; left one firmly adherent. Organs normal.

ALIMENTARY TRACT.

Peritoneum.—Parietal layer pinkish-white, smooth, moist and glistening; 200 c.c. cloudy reddish fluid in cavity. Adhesions in region of cecum and pelvis. Omentum ample, contains normal amount of fat, bile-stained in region of gall bladder.

Intestines.—The small intestine is a pale pink color. From the pylorus to the cecum, beneath the serous coat, are numerous minute grayish-white, raised points, giving a granular appearance to the gut. About midway, within the lumen, is a circular ulcer 2 cm. wide. Ulcer is undermined with ragged edges, which show some thickening. An enlarged gland is present just without at the mesenteric attachment, but not communicating. Bowel is congested in region of ulcer. Large intestine collapsed and no lesions present either without or within.

Stomach.—Organ small and normally situated. No adhesions except at cardia and along lesser curvature. Dissection of this region shows three large caseous lymphatic glands, the largest 4 by 2 cm.; one situated close to the esophagus, one about the middle of the lesser curvature, and the other between these two. The gland in relation with the esophagus has no connection with the stomach wall, but the other two are intimately fused with what proves to be the base of a large ulcer on the inside of the stomach. The outer gland shows calcareous areas, and all are caseous. Several small congested glands are seen around the cardiac orifice, but these are not caseous as are the larger ones. On opening the stomach a large single ulcer is seen in the cardiac end, extending nearly around the esophageal opening and to the middle of the lesser curvature, its outer extent corresponding to the situation of the outer large lymphatic gland. It is covered with a yellowish-white mucoid material. The dimensions of the ulcer are: Length, 9 cm.; width, 4.5 cm. Its edges are irregular, undermined, much thickened, very firm and pale. The floor is cribriform and of varying thickness, measuring at one point 4 mm., at another 1 mm., and at one point only the serous coat is present. Tubercles are not evident in the floor. Dissection from without in, opposite the middle lymphatic gland, just beneath the superficial portion of the floor, shows a calcareous area 2 mm. in diameter, surrounded by a circular zone of pearly white tissue. The mucosa elsewhere shows no ulcers. The lymphatics on the serous coat in the vicinity of the caseous glands and elsewhere show no tubercles.

Esophagus.—Normal.

AUTOPSY—HISTOLOGICAL EXAMINATION.

Liver.—Extreme amyloid degeneration. Tubercles, with giant cells. Round cell proliferation in portal tracts and a high grade of fatty degeneration.

Pancreas.—Section from head shows caseation, but no giant cells. Areas of round cell proliferation in lobules.

Kidneys.—Extensive degeneration of epithelium of convoluted tubules. Marked amyloid degeneration, principally in the tufts. Areas of round cell proliferation throughout. Increase of connective tissue between tubules in pyramidal portion.

Spleen.—Practically all amyloid. Here and there are seen remains of Malpighian bodies with dilated and congested vessels. No tubercles seen.

Intestine.—Sections from ulcer and contiguous tissue show numerous tuberculous areas, varying in size. The centers of these are caseous, with outer zones of lymphoid and epithelioid cells. The most conspicuous condition is a hyperplasia of the connective tissue elements in the submucosa, with areas of adipose tissue and numerous dilated and congested vessels. Giant cells are present, but only occasionally seen. The vessel walls are thickened and show a hyaline degeneration. In places the muscular coat has been infiltrated, and in some places entirely replaced, by the tuberculous process, the latter extending to the peritoneal coat. The base of the ulcer shows superficial necrosis, beneath which is connective tissue, infiltrated with lymphoid and epithelioid cells. Edges of ulcer show chronic thickening. Mucosa of intestine elsewhere shows atrophy of epithelial elements.

Stomach.—Our studies here included examination of section from various portions of the ulcer and stomach wall. The base of the ulcer is for the most part composed of the outer longitudinal muscular coat, though in places there is only the thickened serosa. The gastric surface shows superficial necrosis. Beneath this zone of necrosis is a chronic hyperplasia of the connective tissue, with many lymphoid and epithelioid cells. In some places the muscular coat is entirely replaced by this process. The serous coat is much thickened and infiltrated with lymphoid cells, which are seen in longitudinal columns. Some of the vessels are completely organized and all show thickened walls with a hyaline degeneration. Direct communication can be traced to one of the lymphatic glands through the serous coat. The edges show atrophy, distortion and degeneration of the gland tubules, with a marked proliferation of the interglandular connective tissue. Near the esophagus are areas showing dense aggregations of lymphoid cells with necrotic centers. One of these extends to the surface. No giant cells are seen in any of the stomach sections examined. Tubercle bacilli in small numbers (usually in groups of two or three) are found in the edge of the ulcer. The organ in other portions, but for an atrophy of the mucosa, is normal.

Lungs.—Larger vessels congested and mild grade of capillary congestion. Anthracosis. Alveoli dilated in places, but contain no exudate, cells or débris.

Myocardium.—Normal.

Thyroid Gland.—Normal.

Lymph Glands.—Sections of various lymphatic glands show them to be uniformly necrotic, with occasionally a narrow rim of the gland tissue. No giant cells are seen in any of the glands.

ANATOMIC DIAGNOSIS.

Single tuberculous ulceration of the stomach and intestine; tuberculosis of the abdominal lymphatic glands, liver and pancreas. Amyloid degeneration of spleen, liver and kidneys. Tuberculous peritonitis, involving the visceral layer of the small intestine.

The point of greatest interest in our case is the healthy condition of the lungs, which is most unusual when there is tuberculous ulcer of the stomach. We have found but six similar instances, abstracts of which follow:

CASE 1.—Reported by Besnier.[8] Man, 57 years old, sick three months, greatly emaciated, lower extremities edematous. Nothing found in thorax or abdomen to explain cachexia. The only symptoms: Diarrhea, loss of appetite and vomiting. Autopsy showed tuberculosis of the abdominal glands, with one large gland ad-

8. Bull. Soc. anat. de Paris, March, 1867, p. 97.

herent to the posterior wall of the stomach, this gland having suppurated and perforated into the organ.

CASE 2.—Reported by Paulicki.[9] Man, 41 years old, presenting symptoms of anorexia, repeated bloody vomiting, finally death from peritonitis. Autopsy showed several ulcers near the pylorus, varying in size, the largest, one and one-half inches long, situated on the anterior surface of the stomach, had perforated. Tuberculosis of the glands along the lesser curvature and of the mesenteric glands. Ulcers in the intestines. Few miliary granulations in liver and kidneys. No tuberculosis of the lungs.

CASE 3.—Reported by Hattute.[10] Man, 47 years old, complained of having vomited his food for about eight years. After each meal there was acute pain in the stomach. There would be distension and in from ten to twenty minutes, very rarely at the end of an hour, vomiting would occur. This happened even after small amounts of water were taken. There was marked tenderness over the epigastrium. No melena. Autopsy showed tuberculous peritonitis, marked pyloric obstruction due to a circular mass of granulations similar to those on the peritoneum. Mesenteric and bronchial glands tuberculous. Some pleural adhesions. Lungs healthy.

CASE 4.—Reported by Lava.[11] Man, 26 years old, history of gastric catarrh for three years. Epigastric pain, vomiting and diarrhea. Abdomen became tender to pressure. A painful mass felt in the right hypochondrium. The diagnosis of pyloric stenosis, with probably gastric ulcer was made. Symptoms of acute peritonitis developed and death occurred in twenty-four hours. Autopsy showed a circular ulcer found in the pyloric region which had perforated. Old adhesions between the stomach and intestines. Pyloric glands very large and caseous. Microscopic examination showed typical tubercular structure. No trace of tuberculous process in the lungs or in other organs.

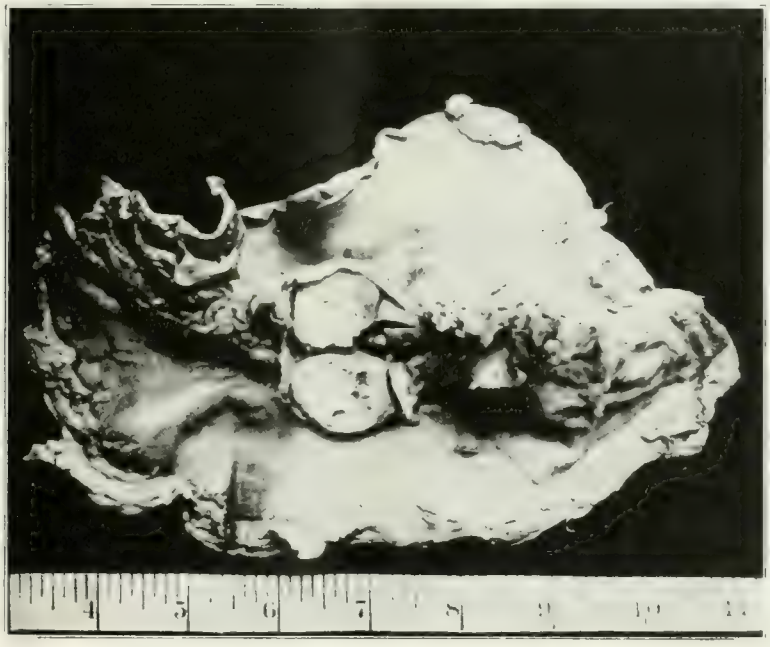
This case was most remarkable in that there was no tuberculous process in other organs.

CASE 5.—Reported by Orlandi.[12] Man, 26 years old, suffered from the age of 14 to 17 with intestinal parasites. Some years later, dyspeptic symptoms developed, at first stomachic, later intestinal. These phenomena grew progressively worse, with rapid emaciation, finally ending in death. Autopsy showed an annular ulcer surrounding and obstructing the pylorus. Neighboring lymphatic glands were greatly enlarged and caseous. Histologic examination proved the ulcer to be tuberculous. There was no trace of tuberculosis of the lungs or of any other lymphatic glands. This was apparently a primary lesion of the stomach.

CASE 6.—Reported by Margarucci.[13] Man, 65 years old, delicate from infancy, had malarial fever and syphilis. Some years earlier he began to vomit after eating, at first without pain. For six years he vomited five or six times a day, sometimes immediately after taking food, more often several hours after. He then had a respite of five months, during which time the digestion was simply labored. The trouble then reappeared and was variable for three years. Soon in addition to vomiting, severe epigastric pain was added, and the vomitus had the appearance of coffee grounds. The stomach became more and more irritable and emaciation rapidly ensued. He never had any cough or fever. There was constipation later, followed by diarrhea. The abdomen was retracted, and marked intestinal peristalsis was visible. Below the xyphoid, deep pressure caused pain

9. Berl. klin. Wchnschr., August, 1867, p. 349.
10. Gaz. d. Hôp., 1874, p. 859.
11. Gaz. med. di Torino, 1893, p. 915.
12. Gaz. med. di Torino, 1893, p. 33.
13. Policlinico, Rome, 1898, p. 75. Sezione Chirurgica.

Internal view of stomach showing ulcer. Organ opened on greater curvature.



External view of lesser curvature of stomach showing caseous glands.

and an ill-defined resistant surface could be felt moving slightly with respiration. Clinical tests indicated pyloric obstruction. Gastroenterostomy and enteroplasty were done, but death occurred two days later. Autopsy showed multiple stenoses of the intestine and stenosis of the pylorus, due to an ulcer which was histologically shown to be tuberculous. The lungs were free from tuberculosis.

The first four cases were cited by Arloing,[3] the last two by Ricard and Chevrier.[4]

SUMMARY.

Our studies show a case of tuberculous infection of the digestive tract, as evidenced by the limitation of the process to the stomach, intestine, liver, pancreas and lymphatic structures draining these organs.

There existed a large single tuberculous ulcer of the stomach, with no involvement of other parts of the organ. This ulcer possessed the usual characteristics of a tuberculous lesion—ragged, thickened, undermined edges and cribriform floor. This was confirmed by histologic examination and the finding of tubercle bacilli in the tissue.

The connective tissue hyperplasia, absence of giant cells and paucity of bacilli in the tissue, speak for an attenuated infective process.

The route of infection seems to have been through the lymphatic system of the gastrointestinal tract. Pulmonary origin has been absolutely excluded by the absence of any tuberculous lesions in the lungs or bronchial glands. This fact was determined with great care, both macroscopically and microscopically.

As to whether the primary seat of infection was the ulcer in the stomach, from which the abdominal lymphatics became infected, or whether the lymphatic glands infected the gastric wall by contiguity, we are unable to say, but the latter seems the more probable.

1315 New Hampshire Avenue.

SEROTHERAPY OF EPIDEMIC CEREBROSPINAL MENINGITIS.

REPORT OF TWELVE CASES.

W. S. CHASE, M.D., AND M. L. HUNT, M.D.
AKRON, OHIO.

In the months of April, May and June, 1907, there were reported to the Health Officer of Akron 22 cases of epidemic cerebrospinal meningitis. The first case came down April 28, the most of them occurring in May and June. The last one was admitted to the hospital September 11, having first shown symptoms six days before.

Four of the patients, strong, healthy young men, were employed at one of the local rubber factories. In no other instance could there be shown any possibility of communication by contact. In fact, a striking feature of the epidemic was the occurrence, at the same time, in widely separated districts of the city, of single cases.

Twelve of the cases were treated at the Akron City Hospital. Of these, 3 of the patients died and 9 recovered, a mortality of 25 per cent. Of the cases outside, one patient recovered and 9 died, a mortality of 90 per cent. All of those treated at the hospital received the Flexner antiserum. Those treated outside did not. The diagnosis of the case of the one outside patient, who recovered, was not confirmed by lumbar puncture and presented atypical symptoms.

While realizing the ease with which the *post hoc* may blossom into the *propter hoc,* when the treatment of any disease is concerned, it seems to us that the striking difference in the mortality rate of these two sets of cases is more than enough to warrant a further and wider trial of the Flexner antiserum.

At the time of the outbreak in Akron the Flexner antiserum had been tried in a few cases at Castalia, Ohio. A supply of this serum was sent to Akron by Dr. Flexner from the Rockefeller Institute of New York, with the understanding that the necessary bacteriologic examinations be made in each case. In order that this might be done under the most favorable conditions, it was decided that the serum should be administered only to patients received at the Akron City Hospital. That fact was communicated to the physicians of the city, and a committee of three physicians from the medical staff of the hospital was appointed to see in consultation the cases of epidemic spinal meningitis admitted, and to have general supervision of the serum administration and of the bac-

teriologic work. That committee consisted of Drs. A. A. Kohler, C. E. Held, and W. S. Chase. They were assisted in their work by Drs. M. L. Hunt and G. M. Logan, the hospital internes.

The diagnosis was made in no case on the clinical signs alone, but these were supplemented, in each instance, by microscopic and culture tests of the spinal fluid withdrawn by lumbar puncture. A puncture was done under aseptic precautions whenever clinical evidence warranted it and as soon as possible after the patient's admission.

In the first few cases the antiserum was not administered until after a microscopic examination of the withdrawn fluid had been made showing the presence of Weichselbaum's *Diplococcus intracellularis*. Later on, when the clinical evidence seemed positive, the injection of the serum was made at the time of the first puncture; but in all cases the clinical evidence was corroborated by the subsequent microscopic findings.

As all the patients were more or less wildly delirious, it was found advisable to perform lumbar puncture, in almost every instance, under general anesthesia. For that purpose chloroform was used. An ordinary aspirating needle was employed, about 10 cm. in length, and, with the patient on his side, with thighs flexed on the abdomen and shoulders brought forward, the needle was inserted about 1 cm. beyond the median line, between the third and fourth lumbar vertebræ. This level is crossed by a line connecting the iliac crests.

The only medication any of the patients received, aside from the injections of serum, was an occasional hypodermic injection of morphin combined with hydrobromate of hyoscin, when delirium and restlessness were pronounced. This was not given to all the patients.

The following synopses taken from the clinical charts while the patients were in the hospital show the progress of each case from day to day:

CASE 1.—*Patient.*—V. H., aged 9, schoolgirl. Referred by Dr. L. R. C. Eberhard. Admitted April 30, 1907, at 9:30 p. m.

History.—Patient first complained of pain in the stomach and legs aching April 28; vomited early in the morning and frequently during the day. She became unconscious about 7 p. m. April 28 and was restless and noisy most of the night. The same conditions prevailed on Tuesday morning, when the family noticed retraction of the head and rigidity of the neck. Tuesday evening patient became worse and more restless, throwing and tossing herself about and screaming. Sordes on tongue, lips and teeth.

Condition on Admission.—Temperature 99.6 F., pulse 100, respiration 24. Unconscious; restless and screaming, especially if touched; pupils moderately dilated but fixed; no nystagmus; plantar, patellar and abdominal reflexes absent; Kernig sign positive; herpes labialis; neck rigidity marked and opisthotonus; sphincters intact.

May 1 and 2: Condition unchanged.

May 2: Temperature 99.6; pulse 100. Lumbar puncture at 9 a. m. yielded 30 c.c. of opalescent fluid; examination showed diplococci, extra- and intra-cellular.

May 3: Condition practically the same as on preceding day, except for loss of sphincter control.

May 4: Condition no better. On lumbar puncture at 10 a. m. 10 c.c. of fluid withdrawn and 10 c.c. of antiserum injected. Convulsions involving left side and face from 10:40 until midnight; chloroform necessary to control; conscious at 8 p. m.; reflexes absent; Kernig present; neck rigid; nystagmus.

May 5: Temperature normal part of the day; pulse 116 to 120. Condition improved; called for milk and water; restless at intervals.

May 7: Temperature and pulse normal. Restless and noisy at times.

May 8: Temperature began to rise and reached 103.6 F.

May 9: Complained of frontal headache. On puncture 30 c.c. of fluid withdrawn; 7.5 c.c. of serum injected. Vomited supper. Reflexes absent.

May 10 and 11: Temperature at or near normal all day; child much improved; not very restless.

May 12: Temperature rose to 104.2; pulse 140. Restless and noisy in the evening; headache. On puncture at 9 p. m. 60 c.c. of fluid withdrawn; 7.5 c.c. of serum injected; stained specimens failed to show diplococci.

May 13 and 14: Temperature at or near normal; greatly improved.

May 15: Temperature 99 to 104 F.; pulse 94 to 136. Puncture at 8 p. m. yielded 20 c.c. of fluid; no serum injected.

May 16: Child not so well; vomited during the day; severe headache and restless.

May 17: Very irritable; noisy and restless; headache; slight abdominal reflex present.

May 19: Knee and plantar reflexes present for first time; Kernig positive. Rational; irritable, but more quiet than usual; calls for food.

May 20 to 25: No marked change, except for some pain in right leg along course of femoral nerve.

May 25: At 10 a. m. 90 c.c. of fluid withdrawn by puncture; 20 c.c. of serum injected; stain negative. At 8 p. m. marked urticaria.

May 26: Temperature normal most of the day; quiet and felt much better; reflexes all present; pain in right leg better; mentality good; involuntary urination. Continued thus for two days.

May 28 to June 3: Temperature ranged between 99 and 103 F.

June 3: Very restless, shouting and crying. At 10 p. m. puncture yielded 75 c.c. of fluid; 15 c.c. of serum injected.

June 4 to 14: Temperature was practically normal; general condition good; rational and moderately quiet most of the time. Reflexes all present and normal; Kernig absent; neck not rigid; perfect function of all parts; no headache; appetite capricious.

June 14: Patient became very restless and noisy. Severe pain in back, leg and abdomen; face flushed; urine and feces involuntary; reflexes all normal; Kernig absent; no neck rigidity.

June 15: At 2 p. m. puncture yielded 75 c.c. of fluid; stain positive; 22.5 c.c. of serum injected. Vomited at midnight.

June 16: Vomited in the morning; refused breakfast; complained somewhat of frontal headache.

June 17: Better to-day; no pain; appetite good.

June 26: Condition good. Reflexes all present and normal; Kernig absent; neck not rigid; no unfavorable sequelæ apparent. Sitting up in bed did not disturb her; less irritable than at any time. Temperature normal from this date on.

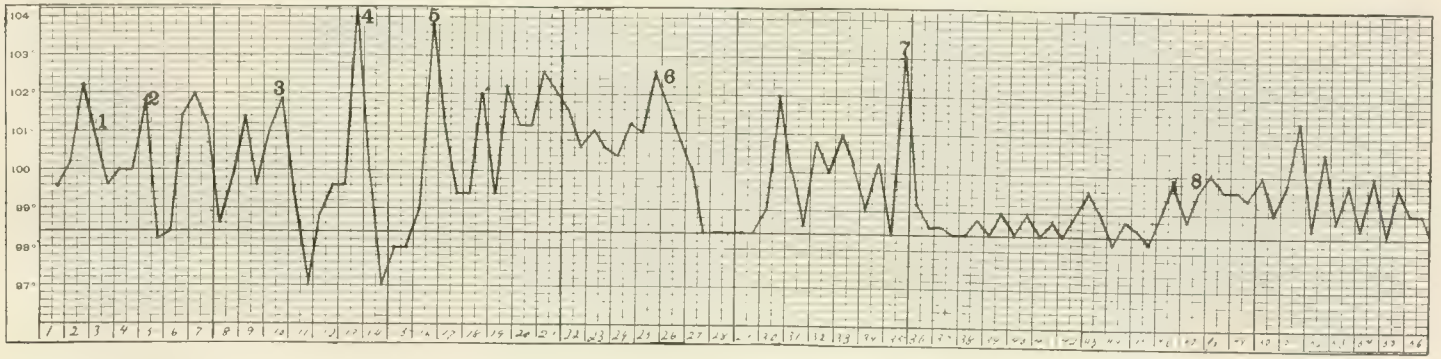


Fig. 1.—Case 1.—(1) 30 c.c. cerebrospinal fluid withdrawn; no antiserum given. (2) 10 c.c. cerebrospinal fluid withdrawn and 10 c.c. antiserum injected. (3) 30 c.c. cerebrospinal fluid withdrawn and 7.5 c.c. antiserum injected. (4) 60 c.c. cerebrospinal fluid withdrawn and 7.5 c.c. antiserum injected. (5) 20 c.c. cerebrospinal fluid withdrawn and no antiserum injected. (6) 90 c.c. cerebrospinal fluid withdrawn and 20 c.c. antiserum injected. (7) 75 c.c. cerebrospinal fluid withdrawn and 15 c.c. antiserum injected. (8) 75 c.c. cerebrospinal fluid withdrawn and 22.5 c.c. antiserum injected.

She began to walk, and July 4 commenced to develop a kyphosis; no angular deformity; spine mobile, not painful; only noticeable when standing; involved the whole length of spine. Gymnastics and massage were instituted and used until July 14, when she was put in plaster jacket. The child made a good recovery, and left the hospital Aug. 6, 1907, 96 days after admission. She has been back to the hospital several times since, and is bright mentally and in good condition.

The clinical symptoms in this case were typical, and it would have been almost impossible for one to make an error in diagnosis depending on them alone. This was the first case in which the Flexner antiserum was used. It was brought from Cleveland by Dr. Ladd, who saw the patient in consultation. There was nothing then to govern the dosage in human beings, but the largest dose which had been given up to that time (10 c.c.) was administered May 4, care being taken to inject no more in volume than the fluid withdrawn. This precaution was afterward disregarded as unnecessary, and the dosage was very materially increased. In spite of the precaution, however, the first injection was followed by convulsions. These were not excited by large amounts later on and did not appear spontaneously. It is, therefore, probable that the association was accidental.

As Flexner and Jobling have pointed out in their article which appeared in the January (1908) number of *Experimental Medicine,* where the first record of the treatment of human beings with this serum is given, it is very difficult to assign a definite effect to the serum in a case so protracted as this. These facts, however, stand out in the history: Within 24 hours following each injection of serum the patient's mental condition was materially improved and the temperature dropped to normal or nearly normal. That improvement was not noticed following a lumbar puncture on May 15, when no serum was injected. Neither was there a fall of temperature nor an improvement in the mental condition when the exacerbations, which occurred periodically throughout the course of the disease, were allowed to go without a lumbar puncture or an injection of serum.

CASE 2.—*Patient.*—H. R., aged 17; rubber worker. Treated by Dr. George Rankin. Admitted May 9, 1907, at 12 m.

History.—Patient was perfectly well on May 8 and worked, but returned home, not feeling well, complaining of headache; was restless the greater part of the night and did not sleep well; vomited during the night, and became unconscious a few hours before admission to the hospital. He also complained of pain in extremities and cramps in legs.

Condition on Admission.—Temperature 101.6 F.; at 11 p. m. temperature was 105.4 F. Pulse 90; pulseless after 2 p. m. Respiration 40; gradually increased to 70 at 10 p. m. Comatose. Pupils: Left contracted, right dilated; did not react to light. Slight nystagmus; plantar, patellar and abdominal reflexes absent; Kernig sign present; no herpes; neck rigid; loss of sphincter control. On

puncture at 3 p. m. 60 c.c. of opalescent fluid withdrawn; stain positive. A second puncture at 11 p. m. gave 60 c.c. of fluid. The antiserum had to be obtained from Cleveland, and none was received until 11 p. m., when 10 c.c. were administered. At that time patient was practically pulseless.

May 10: Temperature at 3 a. m., 106.8 F.; pulseless. Temperature at 5 a. m., 107.2 F.; Cheyne-Stokes respiration; cyanosed; vomited frequently after 12 m. Died at 5:42 a. m.

CASE 3.—*Patient.*—B. S., aged 19; rubber worker. Treated by Dr. W. S. Chase. Admitted May 14, 1907, at 6 a. m.

History.—Patient was well up to May 12, two days before admission to the hospital, when he went to his room complaining of headache. He also had a chill. He was in bed all day May 13; headache worse; vomited and was nauseated; did not eat anything all day. He became unconscious about the time he was moved from his room to start for the hospital.

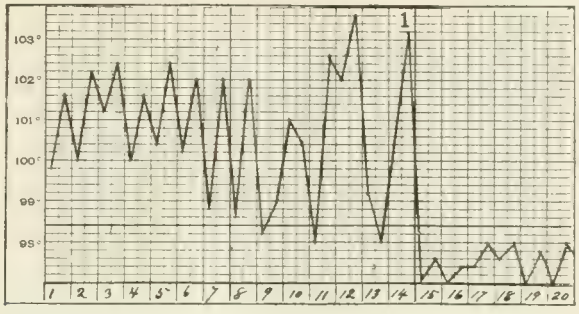


Fig. 2.—CASE 3.—(1) 60 c.c. cerebrospinal fluid withdrawn and 20 c.c. antiserum injected.

Condition on Admission.—Temperature 99 F.; at midnight temperature was 101.6 F. Pulse 56; 9 a. m. to 12 m. pulseless; midnight, 86; markedly cyanosed. Respiration from 32 to 34 and irregular at midnight. Unconscious and wildly delirious; pupils normal; no nystagmus; plantar, patellar and abdominal reflexes absent; Kernig sign positive; no herpes; neck rigid; sphincters intact; urine showed albumin.

May 15: No better. Temperature at 3 p. m., 102.4 F.; pulse 80; respiration 30. Delirious; neck and spine rigid; talking constantly; gets out of bed; passed a round worm 11 inches long.

May 16: No better. At midnight temperature 102.4 F.; pulse 120; respiration 26. Involuntary urination. Puncture attempted, but not successful.

May 17: No better. At 6 p. m. temperature 101.6 F.; pulse 110; respiration 28. Delirious and restless all day. Coughing; face flushed at times; passed a round worm 9 inches long.

May 18: No better. At 3 p. m. temperature 102.4 F.; pulse 98; respiration 28. Delirious and restless.

May 19: Highest temperature 102.2 F.; pulse 108 and weak; respiration 24. Not quite so restless; involuntary urination. Condition continued practically unchanged until May 22, when temperature was normal all day; passed two round worms. Temperature also normal on May 26, but ranged between 99 and 103.6 F. on May 23, 24, 25 and 27.

May 27: Physical examination showed neck rigid; slight return of plantar and patellar reflexes; abdominal reflex absent. Lumbar puncture at 10 a. m., under local anesthesia, yielded 60 c.c. of slightly cloudy fluid; 20 c.c. of antiserum injected; stain showed diplococci.

May 28: Temperature normal all day; patient resting and eating well; apparently in good condition.

May 29: Temperature normal all day; neck rigidity less. Patient continued to improve until June 6, the twenty-fourth day of the disease, when he was able to walk out of the hospital.

CASE 4.—*Patient.*—F. N., aged 32; laborer. Treated by Drs. W. S. Chase and Charles E. Held. Admitted May 16, 1907, at 4:30 p. m.

History.—Patient, who was a strong, hearty man, had always been well. He worked on May 15, but complained of severe headache during the latter part of the day and in the evening. He went to his family physician, who prescribed for his pain, but without relief. On the morning of the 16th he was no better and still complained of severe pain in his head and neck, but had no fever. Morphin, in $\frac{1}{2}$ gr. doses hypodermatically, did not relieve him. A little later he became delirious. Muscular rigidity was marked.

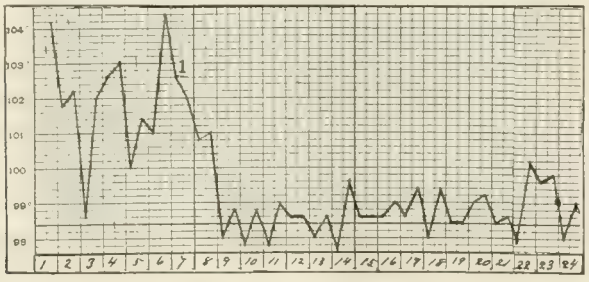


FIG. 3.—CASE 4. (1) 90 c.c. cerebrospinal fluid withdrawn and 25 c.c. antiserum injected.

Condition on Admission.—Temperature 104.2 F.; pulse 124; respiration 30. Conscious at times only; delirious and restless; pupils normal; plantar, patellar and abdominal reflexes absent; Kernig sign positive; no herpes; no neck rigidity; sphincters intact; no nystagmus.

May 17: Temperature at 6 a. m. 101.8 F.; 9 p. m. 102.2 F. Condition slightly improved; conscious at times; noisy and restless; severe pain in head. Urine showed albumin and casts. Put in restraint. Puncture unsuccessful. Pulse weak at times—128 and 134.

May 18: Temperature at 6 a. m. 98.6 F.; pulse 96. At 12 m. temperature 102 F.; pulse 100. Severe pain in head; delirious and noisy.

May 19: Temperature at 6 a. m. 102.6 F.; pulse 116. At 9 p. m. temperature 103 F.; pulse 130. Pain in head severe; delirious and noisy most of the time; hallucinations; respiration 34 to 48 and irregular.

May 20: Temperature at 6 a. m. 100 F.; pulse 110. At 9 p. m. temperature 101.2 F.; pulse 110. Condition the same as on preceding day.

May 21: Temperature at 6 a. m. 101 F.; pulse 106. At 9 p. m. temperature 104.4 F.; pulse 110. Condition not much changed; delirious; restless; talking and hiccoughing.

May 22: Temperature at 6 a. m. 102.6 F.; pulse 98. At 12 m. temperature 102 F.; pulse 98. On puncture with a long needle 90 c.c. of fluid withdrawn; stain showed diplococci; 25 c.c. of serum injected. Pulse irregular.

May 23: Temperature at 6 a. m. 100.8 F.; pulse 96. At 12 m. temperature 98 F.; pulse 90. Patient much improved; conscious and resting quietly all day.

May 24: Temperature normal; condition good, except pain in right arm at times. Urine showed trace of albumin; few casts. Appetite good.

May 25: Temperature normal; no pain; felt well; reflexes all present; Kernig absent; neck slightly rigid.

May 26 to 31: Continued to improve; sat up in bed. Reflexes all present; no pain.

June 1 to 5: Furuncle in right axilla incised. Sat up every day; no pain. Temperature normal.

June 6: Temperature at 6 a. m. 98 F.; pulse 98. At 9 p. m. temperature 100.2 F.; pulse 94. Severe pain in back and legs; unable to move legs; reflexes in legs and feet can not be elicited—rigid; pain and tactile sensation undisturbed.

June 7: Temperature at 6 a. m. 99.6 F.; pulse 114. At 12 m. temperature 99.4 F.; pulse 104. Extremities less painful, except when moved; marked tenderness over large nerve trunks; pain in lower jaw on movement.

June 8: Temperature at 6 a. m. 100 F.; pulse 106. At 9 p. m. temperature 99.4 F.; pulse 104. Felt better; less pain and tenderness not marked. Leucocyte count 22,600.

June 9: Temperature normal; much better; moved legs without pain.

June 10 to 15: Neuritis continued to improve. Discharged, feeling well, June 15, thirty-one days after admission.

Cases 3 and 4 were both marked by a very severe onset. In Case 3 the patient showed extreme cyanosis an hour after admission and was pulseless at the wrist. Diffusible stimulants and oxygen were used freely. These cases are of special interest when compared with some of the others, in that the injections of antiserum were made rather late in the disease. So far as two cases of the same disease can resemble each other they were running the same kind of course. In Case 3 a successful puncture was made on the fifteenth day of the disease. Within 24 hours after an injection of 20 c.c. of antiserum the temperature was normal and the mental condition greatly improved. In Case 4 puncture and injection were performed on the tenth day. Within 24 hours the patient's temperature was normal and he had passed from a period of wild delirium to one of complete consciousness and quiet. It is noteworthy to observe, also, that both patients, save for the neuritis in Case 4, made speedy and uneventful recoveries.

Case 5.—*Patient.*—B. K., aged 15; factory girl. Treated by Dr. L. R. C. Eberhard. Admitted May 16, 1907, at 9 a. m.

History.—Patient had some headache May 15. It was not very severe, but she noticed that she was more nervous than usual. She slept well that night and was conscious on the morning of May 16. Still complained of headache, which was more severe than on the day before. She refused breakfast. Her mother gave her an enema, thinking it would relieve her pain. After this the mother went downstairs and returned in about twenty minutes to find the patient unconscious. The family physician was called and found the patient throwing her-

self around and tossing about on the bed. Rigidity was very marked. She was sent to the hospital at once.

Condition on Admission.—Temperature 103.6 F.; pulse 84 and irregular; respiration 34; comatose; pupils dilated, but reacted; nystagmus; plantar, patellar and abdominal reflexes absent; Kernig sign positive; no herpes; neck rigid; sphincters intact; urine showed albumin. Lumbar puncture gave 45 c.c. of opalescent fluid; diplococci present; 15 c.c. of antiserum injected.

May 17: Temperature at 6 a. m. 99.8 F.; pulse 70; respiration 24. At 12 m. temperature 102.6 F.; pulse 100; respiration 26. Conscious; noisy and restless at times and complained of severe headache.

May 18: Temperature at 6 a. m. 101.6 F.; pulse 94; respiration 20. At 12 m. temperature 100.2 F.; pulse 82; respiration 24. Semiconscious; knee and plantar reflexes present; abdominal reflex absent; Kernig sign present; pain in head severe; noisy at times; involuntary urination.

May 19: Temperature at 6 a. m. 100.8 F.; pulse 90; respiration 20. At 12 m. temperature 102 F.; pulse 96; respiration 22. Semiconscious, but rational when spoken to; herpes labialis appearing; knee and plantar reflexes diminished; abdominal reflex absent; internal squint of both eyes—more pronounced in right. On puncture there was withdrawn 4.5 c.c. of cloudy fluid; 5 c.c. of serum injected.

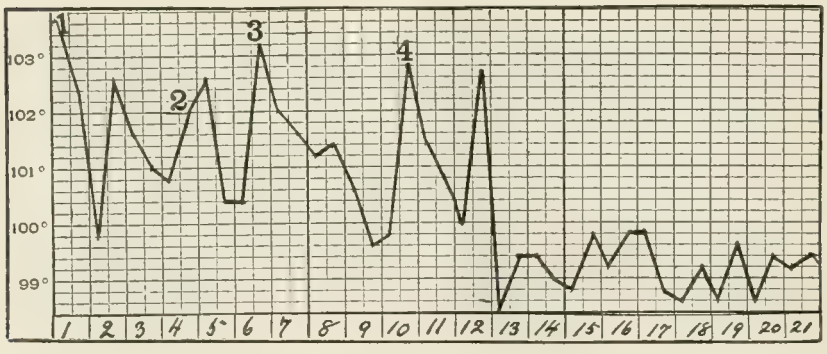


Fig. 4.—Case 5.—(1) 45 c.c. cerebrospinal fluid withdrawn and 15 c.c. antiserum injected. (2) 45 c.c. cerebrospinal fluid withdrawn and 5 c.c. antiserum injected. (3) 4 c.c. cerebrospinal fluid withdrawn and 3.5 c.c. antiserum injected. (4) 75 c.c. cerebrospinal fluid withdrawn and 20 c.c. antiserum injected.

May 20: Temperature 100.8 to 102.6 F.; pulse 106 to 120. About same condition as on day preceding; strabismus not quite so marked; rational when spoken to; unable to move arms; headache severe.

May 21: Temperature in the morning 103.2 F. Puncture yielded 4 c.c. of fluid; 3.5 c.c. of serum injected; stain positive.

May 22: Very irritable; headache severe; pain all over on being moved; herpes on ear; squint not so marked; pupils dilated, react; knee and plantar reflexes present; transient hyperemic areas on abdomen.

May 23: Restless and noisy; severe pain in left leg; unable to move left arm and leg; headache constant.

May 24: Temperature at 6 a. m. 100.6 F.; pulse 120. At 12 m. temperature 102 F.; pulse 100. Semiconscious; irritable; pain in head, left arm and leg; right arm all right.

May 25: Condition same as on preceding day, except decubitus of left head and elbow; tactile and pain sensations normal on left side; 7.5 c.c. of fluid withdrawn by puncture and 20 c.c. of serum injected; stain failed to show diplococci; involuntary urination and bowel movements.

May 26: Temperature at 6 a. m. 101.4 F.; pulse 108. At 12 m. temperature 100.6 F.; pulse 120. Patient better; complains of pain in head at times and is restless and noisy; rational when spoken to; reflexes same as on preceding day.

May 27: Temperature at 6 a. m. 100 F.; pulse 104. At 12 m. temperature 102.6 F.; respiration 26. Reflexes all present; conscious; neck rigid; Kernig sign present; pain in head, arms and legs on movement.

May 28: Temperature 98.4 to 99.4 F. Urticaria on knees and elbows.

May 30: Patient improved. Some headache at times; urine normal; no involuntary urination; knee and plantar reflexes normal; abdominal reflex absent; Kernig sign present; neck less rigid; left arm and leg well; sphincters normal. From this day patient gradually improved, highest rectal temperature being 99.8 F. Her appetite was good and she was free from pain, but she did not gain strength rapidly.

June 8: Kernig sign absent; neck not so rigid; no pain anywhere; felt well, and appetite excellent. She had normal temperature from this date until date of discharge, June 27, being 41 days after admission to the hospital. She was perfectly well in every way, except not as strong as formerly. Patient came to the hospital early in September, feeling all right in every way.

In the light of our present knowledge, it is apparent that the first three injections in this case were entirely too small, especially the second and third. It is uncertain, of course, whether larger doses at these times would have affected the course of the disease, but they should certainly have been given.

CASE 6.—*Patient.*—Z. H., female, aged 17; rubber worker. Treated by Dr. W. S. Chase. Admitted May 19, 1907, at 6 p. m.

History.—Patient had been well, and worked until Saturday noon preceding. She complained somewhat of soreness and aching in the back and legs. At 2 a. m. May 19 she complained of headache and became unconscious about 3 a. m. She was first seen by a physician at 7 a. m. and was reported to have some fever. During the early morning and throughout the day she vomited several times and was unconscious and very restless, continually tossing about, rolling her eyes and head and holding herself in tonic contractures.

Condition on Admission.—Temperature at 6 p. m. 101.6 F.; 99 F. at midnight. Pulse at 6 p. m. 104; 80 at midnight. Respiration at 6 p. m. 28; 18 at midnight. Comatose; pupils equal, moderately dilated and reacted to light; nystagmus; plantar and patellar reflexes present; abdominal absent; Kernig sign present; no herpes; neck rigid; control of anal sphincter lost. Lumbar puncture gave 45 c.c. of opalescent fluid; diplococci present; 15 c.c. of antiserum injected.

May 20: Temperature normal; patient conscious; talked rationally to members of her family at 3 a. m.; some frontal headache.

May 21: Temperature normal; mentality not quite so good; involuntary urination and bowel movements; herpes appearing on lips; hyperemic areas on abdomen. At 9 p. m. 60 c.c. of fluid withdrawn by lumbar puncture; diplococci present; 7.5 c.c. of anti-serum injected.

May 22: Temperature at midnight 99.2 F.; pulse 92; respiration 18. Patient in good condition. Died suddenly at 12:30 a. m. No postmortem permitted.

It will be noted from the history that this patient became unconscious at 3 a. m. on May 19. She was seen by a physician at 7 a. m. and admitted to the hospital at 6 p. m. on the same day. She was given 15 c.c. of the antiserum about an hour after admission. At 3 a. m. the next day her temperature was normal. She had passed from a deeply comatose state to one of perfect consciousness and conversed freely with members of her family. The change was so marked and so impressed the members of the family that they thought a miracle had been performed.

The second injection was given on the evening of May 21, not because her general condition did not seem excellent, but because she was slightly duller mentally than on the day before. She was reported in good condition at 11:30 p. m. An hour later the attending nurse heard her breathing heavily, and in five minutes she was dead. An autopsy was not permitted, and death must be put down to one of those accidents liable to occur at any time during the course of a severe infection. We can not connect in any way her sudden death with the second puncture. She took the anesthetic well and was in good condition after coming out from under its influence.

CASE 7.—*Patient.*—H. S., aged 14; school boy. Treated by Dr. A. F. Sippy. Admitted May 22, 1907, at 8 p. m.

History.—Patient had been well and first complained of headache the evening of May 21. On the morning of May 22 he had vomited twice and complained of severe pain in the head. His temperature was 101 F.; pulse normal. At 5 p. m. he became delirious, with pupils dilated and fixed, but no neck rigidity.

Condition on Admission.—Temperature 104 F.; pulse 120; respiration 44; unconscious; comatose; wildly delirious and noisy; pupils dilated and fixed; no nystagmus; plantar, patellar and abdominal reflexes absent; Kernig sign present; no herpes; neck slightly rigid; sphincters intact. On puncture 75 c.c. of opalescent fluid obtained; diplococci present; 15 c.c. of antiserum injected.

May 23: Improved; semiconscious; temperature 100 F.; pulse 80; respiration 26; restless and noisy at times; rational at times and complained of severe headache.

May 24: Temperature at 6 a. m. 101.8 F.; 9 p. m. 99.8 F. Rational all day; vomited once; severe headache at night.

May 25: Temperature at 9 a. m. 102 F.; pulse 66; respiration 26. On puncture 75 c.c. of fluid obtained; 20 c.c. of serum injected. Rational all day. Temperature at 9 p. m. 98.8 F.; pulse 68; respiration 24.

May 26: Improved; temperature normal all day; pain in head less; reflexes all present; neck rigidity less.

May 27: Improved; temperature at 7 p. m. 98 F.; resting well; some pain in head.

May 28: Temperature at 7 p. m. 99.8 F.; resting well; no pain; neck slightly rigid.

May 29: Temperature at 3 p. m. 100.2 F.; normal at 12 m.; no pain.

May 30: Temperature 100 F. at 12 m., 3 p. m. and 6 p. m.; normal at 9 p. m.; appetite better; no pain.

May 31: Temperature at 6 p. m. 99.8 F.

June 1: Temperature at 3 p. m. 99.2 F.
June 2: From this day on temperature was normal.
June 8: On this day, 18 days after admission, patient sat up in bed three hours. Discharged from hospital.

This case, while not of the fulminating type, was certainly severe. Any one seeing the boy at the time of admission to the hospital would surely have been justified in giving a very grave prognosis. This being the seventh case in our series, the attending physician became bold enough to give the boy 15 c.c. of antiserum at the first injection. The symptoms

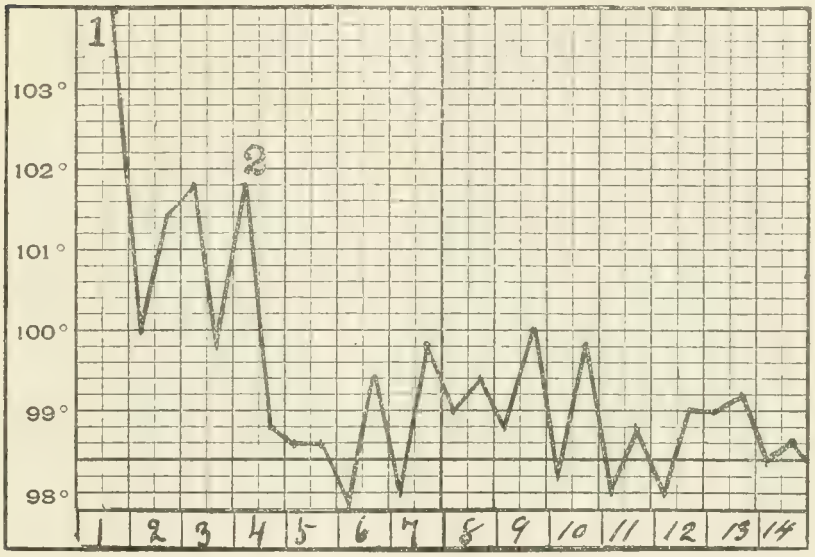


Fig. 5. Case 7. (1) 75 c.c. cerebrospinal fluid withdrawn and 15 c.c. of antiserum injected. (2) 75 c.c. cerebrospinal fluid withdrawn and 20 c.c. antiserum injected.

did not abate so rapidly in this case as in some of the others, and on the fourth day of illness the temperature rose to 103 F. A puncture was made and 75 c.c. of spinal fluid withdrawn. It was then decided to give 20 c.c. of antiserum. In ten hours his temperature was normal and he made an uninterrupted recovery.

Case 8.—*Patient.*—R. M., aged 17; electrician. Treated by Dr. W. S. Chase. Admitted May 25, 1907, at 1 p. m.

History.—Patient, who was an employé of a local rubber company, quit work at noon on May 24 because he did not feel well. He went home, but did not go to bed; refused supper, and later in the evening vomited. He went to bed early, complaining of headache, and was restless the greater part of the night. His headache was worse in the morning. He refused breakfast, and vomited again. About 10 a. m. he became unconscious.

Condition on Admission.—Temperature 105.2 F.; pulse 142; respiration 20; comatose—violent; pupils slightly contracted and reacted to light; no nystagmus; plantar reflex present, patellar slightly exaggerated, abdominal absent; Kernig sign present; no herpes; neck rigid and painful to move; sphincters intact. On puncture 15 c.c. opalescent fluid withdrawn; diplococci present; 15 c.c. serum injected.

May 26: Patient worse. Temperature 102.2 F.; pulse 100; respiration 6; cyanosed; puncture and withdrawal of 15 c.c. of fluid, stain of which showed diplococci. Died shortly after midnight.

CASE 9.—*Patient.*—G. G., aged 17; school girl. Treated by Drs. G. A. Theiss and A. F. Sippy. Admitted June 9, 1907, at 7 p. m.

History.—Patient was well until 24 hours before admission to the hospital, when she began to complain of malaise and headache. She vomited during the night and became unconscious at 2:30 p. m. June 9, just 4½ hours before admission to the hospital.

Condition on Admission.—Temperature 98.4 F.; pulse 108; respiration 20. Unconscious; comatose and very restless; pupils normal; no nystagmus; plantar, patellar and abdominal reflexes absent; Kernig sign positive; no herpes; neck

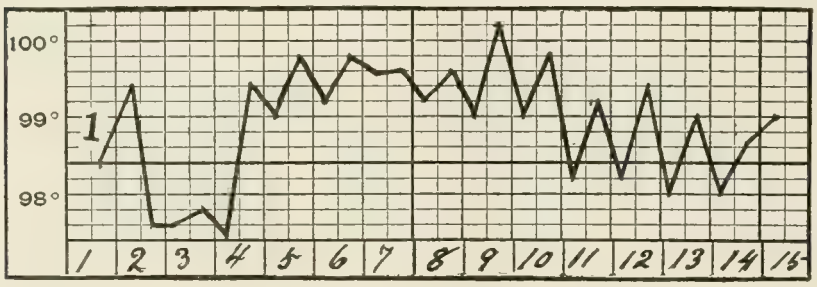


Fig. 6.—CASE 9.—(1) 90 c.c. cerebrospinal fluid withdrawn and 22.5 c.c. antiserum injected.

rigid; sphincters intact. Puncture yielded 90 c.c. of opalescent fluid; stain positive; 22.5 c.c. of antiserum injected.

June 10: Temperature at 6 a. m. 97.2 F.; pulse 102. Temperature subnormal all day; rational at times; slight opisthotonus and nystagmus. It was necessary to use a catheter.

June 11: Temperature subnormal all day; conscious and rational; abdominal and plantar reflexes present; patellar reflex absent; Kernig sign marked; neck rigid; herpes labialis; no pain.

June 12: Highest temperature 99.6 F.; pulse 84. Mental condition excellent; spoke of pain in head only when asked; reflexes all present; Kernig sign present; neck rigid and painful on movement; got out of bed and went to closet alone. Patient gradually improved from the fourth to the twelfth day of the disease. Reflexes all returned. Neck rigidity disappeared. Kernig sign disappeared. Appetite improved. Free from pain most of the time.

June 21: Temperature normal; sat up in chair; ate and slept well; no sequelæ.

June 23: Discharged, 15 days after admission.

The onset in this case was not very severe, although within 24 hours the patient was in a comatose condition and opisthotonus was marked.

All the reflexes were lost. Despite these symptoms and the presence of large numbers of the *Diplococcus intracellularis,* the patient's temperature was normal and the respirations were but slightly accelerated.

CASE 10.—*Patient.*—J. A. S., aged 24; postman. Treated by Dr. George Rankin. Admitted June 24, 1907, at 11 a. m.

History.—Patient had been well, and worked until the day before his admission to the hospital. On that day he attended a picnic and was exposed to the hot sun. He went home in the evening with headache and feeling ill. This he attributed to the effects of the sun. He did not sleep well and was restless, complained more of headache, and became unconscious about 5 a. m. July 24.

Condition on Admission.—Temperature 103.8 F.; pulse 70; respiration 36; comatose and very restless; face flushed; got out of bed; pupils moderately dilated, respond to light; plantar, patellar and abdominal reflexes absent; Kernig sign positive; no herpes; neck moderately rigid; involuntary urination and bowel movements; no nystagmus. Puncture yielded 90 c.c. of fluid; stain positive; 22.5 c.c. of serum injected.

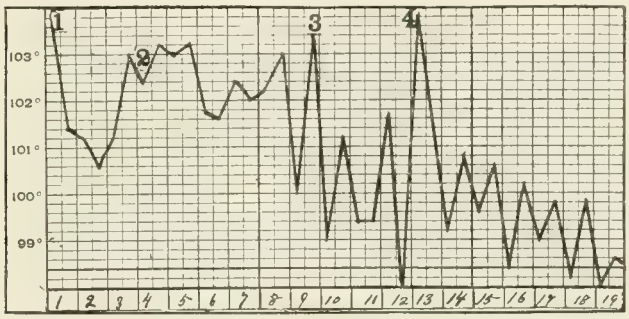


Fig. 7.—CASE 10.—(1) 90 c.c. cerebrospinal fluid withdrawn and 22.5 c.c. antiserum injected. (2) 45 c.c. cerebrospinal fluid withdrawn and 22.5 c.c. antiserum injected. (3) 60 c.c. cerebrospinal fluid withdrawn and 30 c.c. antiserum injected. (4) 45 c.c. cerebrospinal fluid withdrawn and 30 c.c. antiserum injected.

June 25: Temperature at 6 a. m. 101.2 F.; pulse 60. At 12 m. temperature 100.6 F.; pulse 64. Semiconscious; responds when spoken to, but mutters unintelligibly when attempting to form sentences; restless at times; knee reflex absent; plantar and abdominal reflexes present; neck more rigid; Kernig sign present; pupils equal, dilated and respond to light.

June 26: Temperature at 6 a. m. 101.2 F.; pulse 64. At 12 m. temperature 103 F.; pulse 72. Conscious and rational; neck less rigid; some headache.

June 27: Temperature at 6 a. m. 102.4 F.; pulse 70. At 12 m. temperature 103.2 F.; pulse 92. Herpes labialis appearing. At 2 a. m. puncture gave 45 c.c. of fluid; 22.5 c.c. of serum administered. At 9 a. m. rational; singing and talking with other patients; reflexes improved; Kernig sign present; neck rigid; involuntary urination.

June 28: Temperature at 6 a. m. 103 F.; pulse 74. At 12 m. temperature 102 F.; pulse 80. Mental condition good; some pain in back of neck.

June 29: Temperature at 6 a. m. 101.8 F.; pulse 80. At 12 m. temperature 101.2 F.; pulse 74. Same condition as on preceding day. Pain in back of neck and head.

June 30: Temperature at 6 a. m. 102.4 F.; pulse 72. At 12 m. temperature 101.6 F.; pulse 80. Condition good; reflexes all present; Kernig sign present; neck rigid and painful on movement; some headache; herpes labialis extensive and painful.

July 2: Temperature at 6 a. m. 100.4 F.; pulse 70. At 9 p. m. temperature 103.6 F.; pulse 80. Condition the same as on preceding day. At 9 p. m. puncture gave 60 c.c. of fluid; 30 c.c. of serum injected.

July 3: Temperature at 6 a. m. 99 F.; pulse 70. At 12 m. temperature 100 F.; pulse 74. Condition improved; feels better.

July 4 to 6: No essential change, except for pain in testicles; not red or swollen, but very painful to touch.

July 6: Puncture yielded 45 c.c. of slightly cloudy fluid; 30 c.c. of serum injected; stain positive.

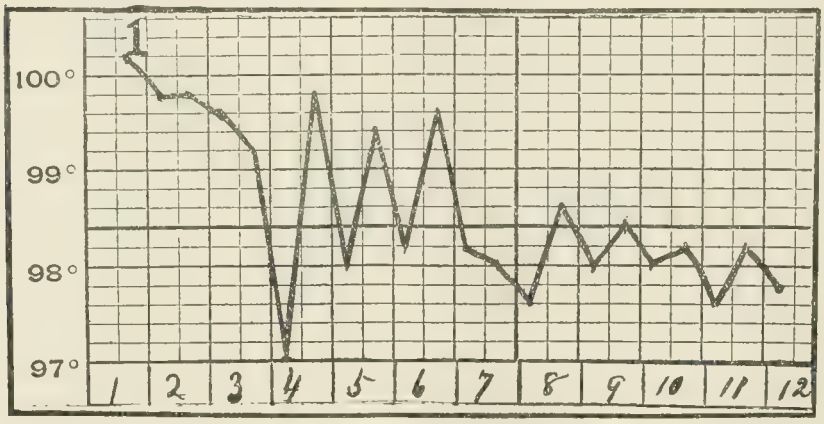


Fig. 8.—Case 11.—(1) 75 c.c. of cerebrospinal fluid withdrawn and 25 c.c. antiserum injected.

July 7: Temperature at 6 a. m. 99.2 F.; pulse 72. At 12 m. temperature 99.8 F.; pulse 84. Patient feels well; no pain.

July 8: Temperature at 6 a. m. 99.6 F.; pulse 80. At 12 m. temperature 99.2 F.; pulse 70. No pain; appetite excellent.

July 9: Temperature normal; no pain; no neck rigidity. Temperature remained normal from this day on.

July 14: Sat up in bed. Patient continued to improve, grew stronger, walked about the ward, and was discharged July 24 at 3 p. m., 31 days after admission to the hospital. Reported since that he can not stand the hot sun; it causes him intense headache.

Case 11.—*Patient.*—E. R., aged 20; machinist. Treated by Drs. C. T. Hill and J. H. Seiler. Admitted June 30, 1907, at 9:50 p. m.

History.—Patient worked all day Saturday preceding, and went to church Sunday morning feeling well. He came home and did not eat much dinner, having a little headache. After dinner he lay down in the yard in the shade for a

while; then went upstairs to bed. He was found about 3 p. m. lying on the floor in an unconscious state, rolling about at times and throwing his hands to his head.

Condition on Admission.—Temperature 100.2 F.; pulse 80; respiration 18; unconscious; comatose; restless, moaning and throwing his hands to his head; pupils normal; no nystagmus; plantar and patellar reflexes exaggerated, abdominal absent; Kernig sign present; no herpes; neck slightly rigid and painful on movement; sphincters intact. Puncture yielded 75 c.c. of opalescent fluid; stain showed diplococci; 25 c.c. of serum injected.

July 1: Temperature at 6 a. m. 99.8 F.; pulse 80; slight convulsion, lasting 20 minutes, at 3 a. m.; vomited several times during the day. Temperature at 12 m. 100 F.; pulse 60; restless and moaning.

July 2: Temperature at 6 a. m. 99.6 F.; pulse 54. Much improved; rational; reflexes all present; Kernig sign less marked; neck still rigid, but not so painful on movement; some pain in head; mentality good. Temperature at 6 p. m. 99.2 F.; pulse 68.

July 3: Temperature at 6 a. m. 97; pulse 62. Condition excellent; only complaint is pain over eyes. Temperature normal most of the day; at 6 p. m. 99.8 F.; pulse 72.

July 4: On this the fourth day of the disease temperature was normal and remained so. Reflexes all present and normal.

July 9: Patient sat up in a chair.

July 11: On this day, 12 days after admission, patient was discharged, walking to the street car.

The onset here was abrupt and severe. This case was received at the hospital earlier than any of the others. From the appearance of premonitory symptoms to the time of the first injection only 12 hours had elapsed. He then received 25 c.c. of serum. Following this early large dose, his symptoms rapidly abated.

CASE 12.—*Patient.*—H. B., aged 6; schoolgirl. Treated by Dr. Charles E Norris. Admitted Sept. 11, 1907, at 1:30 p. m.

History.—Patient attended school Monday, Tuesday and Wednesday, but stayed at home Thursday with a sprained ankle. Friday she suffered with a severe headache; had paroxysms of pain, and put her hands to her head and cried out. She then passed into a semi-comatose state. This continued until Tuesday morning about 11 o'clock, when she went into a comatose state and so remained until the time of her admission to the hospital. On admission her head was not drawn back, but neck was rigid and on attempting to move it her facial expression was that of a person in pain. The same was true in eliciting Kernig's sign. Abdomen was retracted; *tâche cérébrale* present; tongue and mouth dry, and sordes on tongue and teeth. Patient had been treated from Friday until Tuesday for intestinal trouble, and on Wednesday the death sentence was pronounced.

Condition on Admission.—Temperature 102.6 F.; midnight, 103.4 F. Pulse 132; midnight, 138. Respiration 22; midnight, 28. Unconscious; comatose; pupils moderately dilated, but reacted to light; plantar, patellar and abdominal reflexes absent; Kernig sign present; no herpes; neck rigid; sphincter control lost; nystagmus at times. On puncture 35 c.c. of clear fluid was withdrawn, and 30 c.c. of serum injected; stain positive. It was feared that the child would die while the puncture and injection were being made. No anesthetic.

September 12: Temperature at 6 a. m. 103.4 F.; pulse 124. Temperature at 12 m. 101.4 F.; pulse 114. Semi-conscious; respiration more regular; complete

paralysis of legs and right arm, but moved left arm at times. Puncture at 1 p. m. gave 35 c.c. of fluid; 30 c.c. of serum injected; stain positive. Involuntary urination and bowel movements; reflexes absent; neck rigid.

September 13: Temperature at 6 a. m. 101 F.; pulse 110. Temperature at 9 p. m. 100.4 F.; pulse 94. Improved; responds when spoken to; takes nourishment; reflexes all absent. Puncture at 10 p. m. gave 30 c.c. of fluid; 30 c.c. of serum injected. Neck rigid.

September 15: Temperature 99.8 to 100.4 F.; pulse 96. Improved; mental condition better; pronates and supinates left arm; complains of pain on being moved.

September 17: Condition about the same. Neck not so rigid; moves it laterally. Pain on pressure over muscles and large nerve trunks; reflexes absent.

September 19: Somewhat better; enjoys being played with; moves both arms somewhat, also toes; plantar reflex present for first time, others absent; nerves respond to Faradic current; tactile, thermal, and pain senses all present.

September 21: General condition better; plays with doll and laughs. Puncture at 9:30 p. m. gave 40 c.c. of fluid; 30 c.c. of serum injected.

September 22: Temperature at 6 a. m. 101 F.; pulse 108. Temperature at 12 m. 99.2 F.; pulse 112. Condition about the same as on preceding day; somewhat irritable; no rigidity of neck; muscular soreness.

September 23: Moves hands better; abdominal reflex on right side; irritable; small ulcer above inion; plantar reflex present at all times; others absent; no neck rigidity.

September 24: Urticaria over extensor surfaces.

September 26: No change, except for adenopathy on right side of neck.

September 28: Temperature at 6 a. m. 100.4 F.; pulse 116. Temperature at 6 p. m. 102 F.; pulse 136. Adenopathy more marked; moves arms and toes freely and left knee slightly.

September 29: Adenopathy on both sides; sphincter control improved; reflexes the same.

October 4: Urticaria gone; adenopathy more marked. Puncture at 9 p. m. gave 75 c.c. of fluid; 25 c.c. of serum injected. Right side of neck incised and drained; reflexes the same.

October 5: Temperature at 6 a. m., 102.8; pulse, 134. Temperature at 9 p. m., 102.4 F.; pulse, 140. Condition about the same as on preceding day; pain in neck.

October 7: Temperature at 6 a. m., 100.6 F.; pulse, 110. Temperature at 9 p. m., 100.6 F.; pulse, 108. Condition improved; adenopathy improved; no more involuntary urination or bowel movements.

October 11: Condition same as on preceding three days. Puncture at 9 p. m. yielded 65 c.c. of fluid; 15 c.c. of serum injected.

October 12: Internal squint of right eye; pain on being moved; adenopathy disappeared.

October 13: Squint in both eyes; pupils equal and react; erythema on back.

October 15 to 23: Temperature but slightly above normal; moved arms and fingers a little better each day.

October 23: From this day on the child had normal temperature and pulse, was not so irritable, and ceased to have pain on being moved. Her mental condition was good—her people say as good as it ever was. The paralysis improved considerably before she was discharged, so that she was able to feed herself; could invert and evert both feet; moved the left knee very well, and also the toes. She enjoyed sitting up in a wheel chair. She gained about 15 pounds in weight while at the hospital, and her appetite and digestion were good all the time. Reflexes did not improve. On the date of her discharge, plantar reflex was

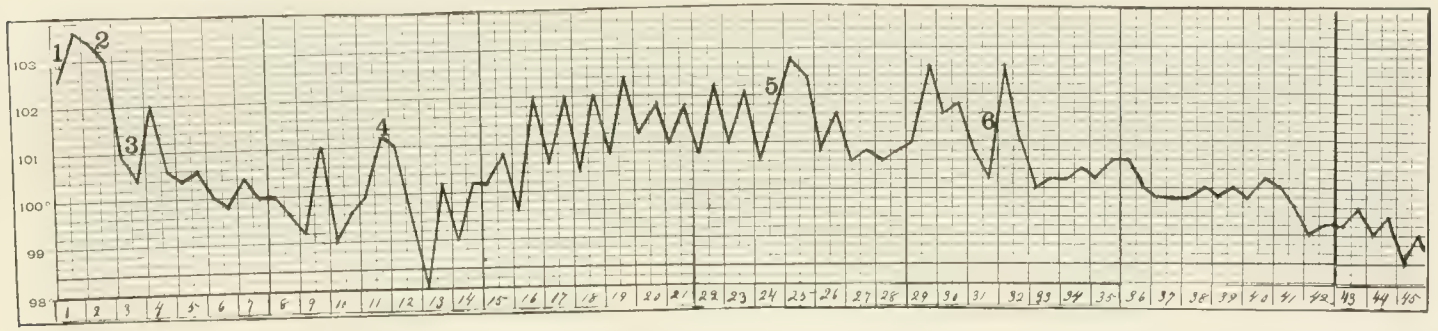


Fig. 9. Case 12.—(1) 35 c.c. cerebrospinal fluid withdrawn and 30 c.c. of antiserum injected. (2) 30 c.c. cerebrospinal fluid withdrawn and 30 c.c. antiserum injected. (3) 30 c.c. cerebrospinal fluid withdrawn and 30 c.c. antiserum injected. (4) 40 c.c. cerebrospinal fluid withdrawn and 30 c.c. antiserum injected. (5) 75 c.c. cerebrospinal fluid withdrawn and 25 c.c. antiserum injected. (6) 65 c.c. cerebrospinal fluid withdrawn and 15 c.c. antiserum injected.

present, patellar absent, abdominal present on right side only; Kernig sign absent. She still had some internal squint of both eyes, but it had improved; pupils equal and reacted to light and accommodation. She knew her letters and could see to read them and also to count. She was discharged Nov. 13, 1907, the sixty-fourth day after entering the hospital.

This case ran a very severe and protracted course. The first puncture was made without an anesthetic of any kind, and 30 c.c. of serum were injected. As stated, the child collapsed under this procedure, and it was thought for a time that she would not revive. On the second and third days thereafter punctures were made and antiserum injected. She was semi-conscious on the second day, rational and able to take nourishment on the third day. It will be noted that a small decubitus ulcer developed over the inion on the thirteenth day, and it was undoubtedly from this source that there resulted an infection of the cervical lymph glands noted in the history. Part of the fever and irritability from the sixteenth to the twenty-sixth day might certainly be attributed to this infection.

Cases.	Day of Disease, First Injection.	Total Number Injections.	Total c.c. of Anti-serum Injected.	Total c.c. Spinal Fluid withdrawn.	Complication.	Sequelæ.	Results.
1	7	6	82.5	390	None. . . .	Kyphosis. .	Recovery by lysis
2	2	1	10.0	120	. . . . .	. . . . .	Death
3	15	1	20.0	60	Nephritis. .	None. . . .	Recovery by crisis.
4	10	1	25.0	90	Nephritis neuritis, furuncles.	None. . . .	Recovery by crisis.
5	2	4	43.5	169	Neuritis. . .	None. . . .	Recovery by lysis.
6	2	2	22.5	105	. . . . .	. . . . .	Death.
7	1	2	35.0	150	None. . . .	None. . .	Recovery by crisis.
8	2	1	15.0	30	. . . . .	. . . . .	Death.
9	1	1	22.5	90	None. . . .	None. . . .	Recovery by crisis.
10	2	4	105.0	240	None. . . .	Headache in sun.	Recovery by lysis.
11	1	1	25.0	75	None. . . .	None. . . .	Recovery by crisis.
12	6	6	160.0	275	Adenitis, strabismus, paralysis of extremities.	Partial paralysis of extremities.	Recovery by lysis.

CONCLUSIONS.

Although the figures given above record 75 per cent. of recoveries in cases treated with the antiserum, we feel that it is really unfair to put Case 2 in the failure column, for the serum was not used until some time after the patient had become pulseless. In Case 6 the improvement following the first injection was as marked and as satisfactory as in any of those which went on to recovery. Death came suddenly and without a warning. The remaining case which resulted fatally was of the most pronounced fulminating type.

While we have not the clinical records of the cases outside the hospital which did not receive the antiserum, all of which died but one, we certainly have the right to assume that, occurring in the same epidemic, the difference in mortality in these cases as compared with those that received the antiserum was not due simply to their having been of much greater average severity.

THE PRESENCE OF ANTAGONISTIC SUBSTANCES IN THE BLOOD SERUM IN EARLY AND LATE SYPHILIS AND IN PARESIS AND TABES.*

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The appearance of the work of Wassermann, Neisser and Bruck,[1] and of Wassermann, Neisser, Bruck and Schucht[2] describing a positive serum reaction in syphilis by means of Wassermann's modifications of the Bordet-Gengou method of complement binding, gave an impetus to the study of serum reactions in syphilis, paresis and tabes, and of the diagnostic value of the results obtained. The reaction of Wassermann, Neisser and Bruck is based in principle on the specific binding of complement, such as occurs, for instance, in the presence of an immune precipitin containing serum and the corresponding precipitinogen. In the reaction the antigen is represented by an extract of the liver of a syphilitic fetus, and the antibody is contained in the blood serum of a syphilitic patient or in either the blood serum or cerebrospinal fluid, or both, of a paretic or tabetic patient.

To carry out a test for the reaction one mixes in test tubes definite quantities of the liver extract and the inactivated blood serum (or cerebrospinal fluid) and adds complement. After standing one hour in the incubator to allow for the binding of the complement, an inactive immune hemolytic serum, with its corresponding corpuscles, is added and the tubes are returned to the incubator, where they remain for two hours. At the end of this length of time they are taken out and examined for evidences of hemolysis. A final opinion, however, as to the presence and degree or absence of hemolysis is best deferred until after the tubes shall have remained over night in the ice chest. In the case of a positive reaction, the evidence that complement has been bound and thus diverted from the hemolytic amboceptor of the immune serum is afforded by the fact that hemolysis has not occurred.

As in other hemolytic experiments, perhaps even to a greater extent than in those, it is essential that a number of control tests be made. For example, in addition to the customary system controls, the extract and serum should be tested separately for both hemolytic and anti-hemolytic

* From the Rockefeller Institute for Medical Research, New York.

1. Deutsche med. Wchnschr., 1906, xxxii, 745.

2. Ztschr. f. Hyg. u. Infektionskrankh., 1906, lv, 451.

effect, and together, without the addition of complement, for hemolytic effect. Furthermore, it should be shown that the liver extract with normal or non-syphilitic serum does not bind complement, etc.

As regards the nature of the substances on whose interaction the binding of complement depends, there exist certain differences of opinion. Without discussing the question at length, it may be said that Wassermann believed in the beginning that the substances were directly related in origin to *Spirochæta pallida*. Later he held that the reaction is only a serum diagnosis of some substance which was formerly unknown to us, and which stands in some relation to the syphilitic infection. Citron,[3] on the other hand, while fully confirming the specificity and diagnostic value of the reaction, believes that the nature of the substances can not be determined definitely until the spirochete has been grown in pure culture. Nevertheless, he suggests that during the course and in consequence of the syphilitic infection certain products of cell metabolism may lead to auto-immunization, and that it may be to these substances, with their corresponding antibodies, that the reaction is due. According to Levaditi and Yamanouchi,[4] the antigen may be represented by sodium taurocholate and glycocholate, and to a less extent by lecithin. Finally, Weil and Braun[5] believe that some substance besides lipoids may be responsible for the reaction, inasmuch as they obtained it with extracts of liver, from which the lipoids had been removed by repeated shaking with petroleum ether.

Notwithstanding the doubt which surrounds the cause and nature of the Wassermann reaction in syphilis, its value as a diagnostic means would seem to have been confirmed by the observations of Detre,[6] Citron,[7] Marie and Levaditi,[8] Meier,[9] Michaelis and Lesser,[10] and many others. In considerably more than 1,000 cases of syphilis in all stages, in paresis and in tabes a positive reaction has been obtained in approximately 80 per cent. of the number. While with normal and non-syphilitic serum the occurrence of the reaction has been reported only once, namely, in frambesia tropica, by Blumenthal.[11] This last result is less surprising when we consider the similarity which yaws bears to syphilis.

3. Berl. klin. Wchnschr., 1907, xliv, 1370.
4. Compt. rend. Soc. de Biol., 1907, lxiii, 740.
5. Wien. klin. Wchnschr., 1908, xxi, 151.
6. Wien. klin. Wchnschr., 1906, xix, 619.
7. Deutsche med. Wchnschr., 1907, xxxiii, 1165.
8. Ann. de l'Inst. Pasteur, 1907, xxi, 138.
9. Berl. klin. Wchnschr., 1907, xliv, 1636.
10. Berl. klin. Wchnschr., 1908, xlv, 301.
11. Deutsche med. Wchnschr., 1908, xxiv, 258.

As has been pointed out, this reaction is concerned mainly, at least from a clinical standpoint, with the demonstration of an antibody. To be sure Wassermann, Neisser, and Bruck[1] drew attention to the fact that the ability to demonstrate antigen in the body fluids of syphilitics would be of considerable importance in diagnosis and treatment. They even succeeded in doing so in a few instances in which they used as an antibody-containing fluid the serum of apes immunized with syphilitic material. Usually, however, the attempt has failed; possibly, they suggest, on account of the difficulty of obtaining a sufficiently strong immune serum.

Recently Fornet, Schereschewsky, Eisenzimmer and Rosenfeld,[12] by means of a direct method, as opposed to the above, which may be considered as an indirect one, claim to be able to show the presence of either syphilitic antigen or antibody in the blood serum. The method is essentially that advocated by Ascoli in carrying out the usual precipitin test. On bringing into contact the serum from a patient with early syphilis and that from a paretic or tabetic, Fornet observed a delicate ring of cloudiness at the zone of contact. The ring never occurred when either pathologic serum in the test was replaced by a normal serum. The cloud is due, according to Fornet, to the precipitate which results from the interaction of "lues-precipitinogen," arising directly from the spirochetæ themselves, and its corresponding "lues-precipitin." Inasmuch as the production of precipitin demands the preceding occurrence within the organism of precipitinogen, Fornet concludes that it is precipitinogen which is present in early syphilis and precipitin in later conditions as in paresis and tabes. In a few instances he found precipitinogen in paresis and tabes, i. e., the serum from one paretic or tabetic gave a ring with the serum from another. This apparent discrepancy is explained by the assumption that in the instances where precipitinogen was present the syphilitic process was still active within the body.

Assuming the correctness of the observations and deductions of Fornet and his associates, it would appear that complement would be bound if added to a mixture of serum derived from a patient with early syphilis (presumably containing precipitinogen) and serum derived from a paretic or tabetic (presumably containing precipitin), since it is always bound in the presence of a specific precipitin reaction. Indeed, in view of the extreme delicacy of the binding reaction (Neisser and Sach's modification of the forensic precipitin test), it might be expected to reveal the presence of quantities of precipitinogen in syphilis too minute to produce

12. München med. Wchnschr., 1907, liv, 1471; Deutsche med. Wchnschr., 1907, xxxiii, 1679.

a visible precipitate. Consequently, in our attempts to show the presence of antagonistic substances in the two varieties of sera, we have used both the methods of complement deviation and precipitation.

Material was placed at our disposal through the kindness of Dr. Moore of the Manhattan State Hospital and of Drs. Mitchell and Eckert of the City Hospital. The sera of nineteen individuals were tested in various combinations. From patients with secondary syphilis with active manifestations there were seven specimens; from tertiary syphilis (gumma), one specimen; from paresis, four specimens; tabes, one specimen, and from normal persons, six specimens. In the binding experiments, the technic of Wassermann and his pupils was followed, except that the liver extract was replaced by serum from a patient with secondary syphilis. The results of these tests were uniformly negative, as is shown in Table 1:

TABLE 1.

						Result.
Serum	M., secondary syphilis	+	Serum	W. A., paresis		Negative
Serum	J., secondary syphilis	+	Serum	W. A., paresis		Negative
Serum	V., secondary syphilis	+	Serum	M., tertiary syphilis		Negative
Serum	J. S., secondary syphilis	+	Serum	R., tabes		Negative
Serum	J. S., secondary syphilis	+	Serum	R. B., paresis		Negative
Serum	J. S., secondary syphilis	+	Serum	T. C., paresis		Negative
Serum	J. T., secondary syphilis	+	Serum	W. P., paresis		Negative
Serum	M., secondary syphilis	+	Serum	J., normal		Negative
Serum	W. A., paresis	+	Serum	J., normal		Negative
Serum	V., secondary syphilis	+	Serum	M., normal		Negative
Serum	M., tertiary syphilis	+	Serum	M., normal		Negative
Serum	J. S., secondary syphilis	+	Serum	C., normal		Negative
Serum	R., tabes	+	Serum	C., normal		Negative
Serum	J. S., secondary syphilis	+	Serum	G., normal		Negative
Serum	R. B., paresis	+	Serum	G., normal		Negative
Serum	T. C., paresis	+	Serum	G., normal		Negative

The sera were employed in quantities of 0.2 c.c. and 0.1 c.c. In each experiment, the following control tests were made:

TABLE 2.

Serum 1.	Serum 2.	Complement guinea pig.	Immune rabbit serum, anti-sheep.	Sheep's corpuscles, 5 per cent.	Result in terms of hemolysis.
0.3	...	...	.....	1	—
...	0.3	...	.....	1	—
0.2	0.1	...	0.002	1	—
0.3	...	0.1	0.002	1	+
...	0.3	0.1	0.002	1	+
...	...	0.1	0.002	1	+
...	...	0.1	.....	1	—
...	...	...	.....	1	—
...	...	...	0.002	1	—

The results with the precipitate reaction in contrast to the above were not uniform, but quite variable and indecisive. Nine tests were made with serum from patients with secondary syphilis (supposed to

contain precipitinogen) and serum from patients with tertiary syphilis, paresis and tabes. Of these, three were positive and six negative. Normal serum was tested with the serum from patients with secondary syphilis six times, with three positive and three negative results; with one serum from tertiary syphilis, with positive result; with one serum from tabes with negative result, and with three sera from paresis, with one positive and two negative results. Twice the serum from one patient with secondary syphilis was tested against the serum from another patient in the same stage of syphilis, with one positive and one negative result. And, finally, one normal serum was tested in the undiluted state with its own dilutions of one to five and one to ten. Table 3 shows the inconstancy of the results.

TABLE 3.

Serum S. secondary syphilis.			Serum T C. paresis.			Serum R. B. paresis.			Serum G. normal.			Result. After.	
Native.	1 to 5.	1 to 10.	Native.	1 to 5.	1 to 10.	Native.	1 to 5.	1 to 10.	Native.	1 to 5.	1 to 10.	2 hours.	16 to 20 hours.
×	.	..	×	..	..	.	..	..	..	..	..	—	—
×	.	..	..	..	..	×	..	..	..	..	.	—	—
×			.	..	.	.	.	..	×	..	.	—	—
..	.		×		.	.	.	..	..	..	.	+	+
	×				.	×	.	..	..	..	..	+	—
	×												
..	..	..	.	..	..	.	.	.	×	..	.	—	—
×		.		×	..			.	.	..		—	—
×	.	.			..		×	.	..	..	..	—	—
×		.	.	.	..			..	..	×		+	—
×					×		..	..	.	..	.	—	—
×	.	.	.	.	.		.	..	.	..	×	+	—
		..	×	..	..	.	..	..	..	..	×	—	—
					.	×		..	.	..	×	+	+
		.	×	..	..			.	×	..	..	—	—
				.		×		.	×		.	—	—
		.	×	.	..		.	..	..	×	.	—	—
		..	.	..	.	.		..	×	×	..	+	—
..	..	..	..	..	..	..	..	.	×	..	×	+	+

In employing the test, it is absolutely necessary that the sera be perfectly clear. On account of the delicacy and fineness of the rings, a certain amount of practice is required for a correct reading of results. Sometimes in our experiments the rings appeared within two hours, sometimes not until the following morning, and sometimes those which appeared within two hours persisted until the following morning and sometimes not. With two exceptions the cloud appeared only when one or the other serum was employed in the diluted state. A temperature of 37 C. seemed to have no effect on the reaction. While not attempting to explain the occurrence of the rings, whether they are merely optical phenomena or

real precipitates of some undetermined substance, we feel unjustified in believing that they are necessarily the result of a specific reaction between lues-precipitinogen and lues-precipitin.

Recently Plaut, Heuck, and Rossi[13] have reported results with the precipitate reaction which are quite similar to those described above. With the combination of serum from syphilitic patients and serum from paretics they reported six positive and ten negative results; with serum from syphilitic patients and normal serum, four positive and four negative results; with normal serum and serum from paretics, six positive, five negative. Two experiments, in which the serum of one patient with secondary syphilis was tested with the serum from another patient with secondary syphilis, gave negative results. Of two tests with serum from one normal person and serum from another normal person, one was positive and one negative. Finally, when one normal serum was tested with its own dilutions there were three positive results and one negative result.

They believe that the ring of a positive reaction is an actual precipitate, but of what nature they are not prepared to say. The difference in the density of the two media appeared to have an influence upon the occurrence of the reaction, since in their tests a positive result was never obtained when both sera were used undiluted. Although considering it possible that by means of precipitation a specific reaction for syphilis may be found, they conclude that in its present form the precipitate reaction has no place in diagnosis.

CONCLUSION.

Neither by the complement-binding method nor by the method of precipitation as at present carried out is it possible to show the presence of antagonistic substances in the blood serum of patients in the secondary stages of syphilis on the one hand and in the tertiary stage on the other, or in such parasyphilitic affections as paresis and tabes.

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13. Münch. med. Wchnschr., 1908, lv, 66.

CLINICAL MANIFESTATIONS OF HEMORRHAGIC RENAL INFARCT.

REVIEW OF LITERATURE. REPORT OF A CASE.

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While a most thorough knowledge regarding the pathology of renal infarct exists to-day, as a result of the classical studies of Virchow, Rokitansky, Cohnheim, Litten, Ribbert and others, very little has been said or written about its clinical manifestations. This undoubtedly must be attributed to the fact that renal infarct, as a clinical entity, is extremely rare, and that, while small infarcts are not infrequently found postmortem, they are very rarely manifested clinically.

To quote Senator: "Symptoms referable to hemorrhagic infarction of the kidney are rarely observed unless the infarcts are unusually large or numerous, when there may be well marked symptoms, of which sudden pain in the corresponding kidney, aggravated by pressure, and the appearance of blood and hemoglobin in the urine, are somewhat characteristic."

Leube makes the following statement: "Cases where hemorrhagic kidney infarcts were diagnosed antemortem are very rare. I was able to diagnose the condition in only one case."

The experience with my own case and careful study of cases from the literature convinced me that renal infarcts, while rarely sufficiently large, are capable, at times, of producing a sharply cut clinical picture of their own, and are, therefore, worthy of special study.

A few words regarding the causation of renal infarcts may not be amiss here.

Renal infarction can be produced by occlusion of the renal artery itself or of one or several of its branches. Occlusion of the renal artery may be the result of an autochthonous thrombosis from local causes or it may be due to embolism. By far the most common cause is arterial embolism. The causes are the same as those of embolism elsewhere—the lodgment of clots, of inflammatory deposits from the left side of the heart or from the aorta, particles of tumors, micro- and macroparasites, particles of pigment and of calcium that have gotten into the arterial circulation. Diseases of the left side of the heart are the predominating etiologic factors, as will be seen from the review of cases. Arterial thrombosis is extremely rare in the renal arteries, and, as in the case of

other arteries, it is the result of diseases of the vessel wall, particularly endarteritis, arteriosclerosis, amyloid degeneration, and injury to the coats.

REVIEW OF LITERATURE.

Traube, in 1856, was the first to diagnose and report a case of renal infarct. Leube mentions one case, which he diagnosed, in his "Specielle Diagnose der inneren Krankheiten" (1891, p. 325).

Four more cases reported by various authors were diagnosed post-mortem. Rudolph Schmidt was really the first clinician who made a thorough study of this condition. He reported three cases from Neusser's clinic, all of which he diagnosed antemortem. An idea of the meagerness of literature on the subject can be gathered from the fact that I was able to collect only ten cases, besides my own.

With regard to etiology these cases group themselves as follows: (1) Those due to arterial embolism, the result of a valvular lesion of the heart; (2) those due to arterial embolism, the result of an infectious process other than endocarditis; (3) those due to local arterial disease, with thrombus formation. The last group is represented by only two cases—one case reported by von Recklinghausen, in which the thrombus formation was due to injury of the renal artery, and by my own case, in which the thrombus formation was the result of an obliterating endarteritis of the renal arteries and their branches. The second group includes two cases, while the first comprises the remaining seven.

CASE 1.—(Traube[1]). *History.*—This celebrated case occurred in a machinist, 18 years old, who suffered from aortic insufficiency combined with dilatation and hypertrophy of both ventricles. On October 14 the patient was awakened from sleep at 1 a. m. by a very intense pain in the region of the right kidney. The pain radiated into the right thigh. There was some suppression of urine, but no albumin or blood. The pain subsided considerably. On October 19 there was sudden onset of vomiting, with general collapse. Death occurred four days later, preceded by marked anxiety, restlessness and air hunger.

Autopsy.—Warty vegetations on the semilunar valves. Spleen contained one infarct size of a hazelnut. Both kidneys contained numerous small infarcts. The right kidney contained one large infarct which protruded slightly above the cut surface. The infarct measured two inches at its base and extended to the hilus.

CASE 2.—(Bartels[2]). *History.*—Boy, 8 years old, tracheotomized for croup, suddenly developed pain in the region of the spleen, followed by enlargement of the organ. Several days later he developed pain in the left thigh, followed shortly by paralysis of the extremity. There were no urinary symptoms. Patient died four days after onset.

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1. Ueber den Zusammenhang von Herz und Nierenkrankheiten, Berlin, 1856, p. 77.

2. Cited from "Untersuchungen über die Embolishe Processe, von Dr. Jul. Cohnheim," 1872.

Postmortem.—A large infarct of the spleen. Right kidney normal. Left kidney contained a large infarct. Left renal artery and its branches were thrombosed. There was no endocarditis.

CASE 3.—(Yuhel Renoy[3]). *History.*—Girl, 16 years old, convalescing from scarlatina. Developed pain in both lumbar regions on the second day of normal temperature. Pain was not very intense. She was catheterized daily without result. Patient died after six days of total anuria, but without uremic symptoms.

Autopsy revealed no cardiac or aortic lesion. Both kidneys were entirely necrosed. Multiple emboli were found in the renal arteries and in the glomerular tufts.

CASE 4.—(von Jurgensen[4]). *History.*—A woman, 27 years old, suffering from a double mitral lesion. This patient had three attacks of pain from November 8 to January 29. Pain was on the right side, ushered in suddenly and accompanied by marked albuminuria, but no blood. Each attack lasted from three to four days.

Autopsy.—Endocarditis, new vegetations engrafted on an old valvular lesion. Infarction of spleen. Left kidney was normal in size and contained small cortical infarcts. Right kidney was about one-fourth the normal size, and almost entirely necrotic. The right renal artery was completely blocked by red thrombi.

CASE 5.—(von Leube[5]). *History.*—Cabinet maker, 17 years old. Suffered from recurrent attacks of rheumatic arthritis. Showed aortic insufficiency. This patient had two attacks of pain in both kidney regions. Urine, previous to each attack, was normal. With each attack there appeared blood and albumin. Case was diagnosed as one of renal infarction. Patient recovered.

CASE 6.—(R. Schmidt[6]). *History.*—Laborer, 40 years old, suffering from recurrent attacks of rheumatic arthritis, associated with mitral insufficiency, suddenly developed a very intense pain in the right lumbar region. Pain did not radiate to genitalia or thigh, and was increased on palpation. There were no urinary changes. Diagnosis of infarct of the right kidney was made.

Autopsy showed a double mitral lesion, fresh anemic infarcts of the right kidney with hemorrhages into the capsule.

CASE 7.—(R. Schmidt[6]). *History.*—A girl, 21 years old, who had had four attacks of acute rheumatic arthritis, and who also had symptoms of mitral stenosis, developed a sudden pain, first in the left lumbar region, later in both right and left. In the previously normal urine there were found red cells and albumin, the latter in abundance. There was also a marked oliguria, the patient passing about 200 c.c. in twenty-four hours. Was diagnosed as bilateral kidney infarction.

Autopsy.—Endocarditis, double mitral lesion. Splenic infarcts. Numerous infarcts in both kidneys, largest 4½ by 1 cm.

CASE 8.—(R. Schmidt[7]). *History.*—Male, 45 years old, suffering from a double mitral lesion, developed a sudden severe pain, first in the right, later in both right and left kidney regions. There was suppression of urine with albumin, casts, and few red cells. Pain subsided four days later. Two days after subsidence of pain the patient developed a right sided hemiplegia and died from symptoms of cerebral apoplexy.

Antemortem *diagnosis* was, bilateral kidney infarction, embolism of the left Sylvian artery.

Postmorten findings established the correctness of the clinical diagnosis.

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3. Traite de Medicine, v, 643.
4. Nothnagel's Handb., xv, 105.
5. Specielle Diagnose der inneren Krankheiten, 1891, p. 325.
6. Wien. klin. Wchnschr., 1901, p. 451.
7. Wien. klin. Wchnschr., 1902, p. 643.

CASE 9.—(Georg Riebold[8]). *History.*—Servant girl, 29 years old, suffering from broken compensation due to double mitral lesion, the result of an old articular rheumatism. Two months after admission to hospital was suddenly seized with a very intense pain in the left side. Pain was well localized and did not radiate. It subsided slowly in the course of two days. There was retention of urine and some suppression, but no albumin, blood, or casts. There was slight fever and a leucocytosis of 21,600. On the third day, the patient developed pain in the corresponding region on the opposite side. On the fifth day she developed paresis of the right arm and leg and of the lower branches of the right facial nerve. Died on the sixth day of respiratory paralysis.

Postmortem Findings.—Mitral stenosis and insufficiency. Embolism of the basilar artery. Upper half of the left kidney infarcted, lower containing several small infarcts. Injection of the perirenal tissue. Embolus of the left renal artery extending into its upper branch and occluding it. Several small infarcts of the right kidney. Spleen contained an infarct, size of a cherry.

CASE 10.—(von Recklinghausen[10]). *History.*—In this case was found post mortem, in a boy who died eight days after sustaining severe internal injuries—the result of a fall—a circular injury to the coat of the left renal artery. This was about two lines in length and one in width; ½ cm. below this was a large red thrombus. All of the branches of the artery were likewise thrombosed. The kidney was entirely necrosed. This case established two important points: (1) That kidney infarcts may be produced by trauma to renal vessels; (2) that formation of typical necrotic infarcts is accomplished in a relatively short time.

CASE 11.—(Author's Case). *History.*—Man, 44 years old, married. Entered Michael Reese Hospital, Nov. 29, 1905, giving the following history: One year ago, after a drive on a cold day, he experienced painful, cramp-like sensation in the big toe of the left foot. Since then had occasional cramp-like sensations in the toe. Five weeks ago pain became very severe. Examination showed lividity of the lower third of the leg and of the foot. Heart was normal, urine negative. Gangrene of the big toe and later of the other toes and of the foot followed within a short period of time. Patient suffered most agonizing pain and was kept almost continually under the influence of morphin. Gangrene steadily progressed upward. The condition was then diagnosed as Raynaud's disease. Three weeks after admission patient developed high temperature, rigors, sweats and cough.

Examination.—Several foci of dulness and harsh breathing were found in the lungs. An ascending thrombophlebitis, proceeding from the gangrenous area upward, was detected. Urine now showed albumin and casts, but no blood. The presumption was that the patient had infected himself by scratching the painful foot. The extremity was amputated, and the patient recovered in about two weeks. He re-entered the hospital July 2, 1907, after a lapse of eighteen months, complaining of a continuous pain in the left upper quadrant of the abdomen of two weeks' duration, vomiting every morning, and cramp-like pain in the calf. During this second stay in the hospital the man had two attacks of pain, each lasting about four days. They were characterized by severe pain and tenderness in both lumbar regions during the first attack and in the right lumbar region during a second attack. They were accompanied by profuse vomiting, severe headache, slight fever and leucocytosis (as high as 28,000).

Urinalysis.—Spec. gr., 1.018; marked trace of albumin, hyaline, granular and epithelial casts; a few red cells and some hemoglobin. The last two were never observed previous to the onset of abdominal pain.

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8. Deutsches Arch. klin. Med., 1905, lxxxiv, 498-517.
10. Virchow's Arch. f. Path. Anat., xx, 205.

On the morning of October 6, having retired the previous night in an apparently normal state of health, the patient was awakened from sleep at about 6 o'clock by a severe pain in the left upper quadrant of the abdomen. The pain was of a stabbing rather than of a colicky character. It was so severe as to cause the patient to throw himself about in a helpless fashion and to cry out loudly. The pain was confined to a rather small area in the left anterior lumbar region, below the twelfth rib, and from there radiated towards the median line in front. There was no radiation along the course of the ureter, to the penis, the scrotum or the thigh. He vomited profusely and complained of severe occipital headache.

Examination showed a very well developed and well nourished man. The abdominal wall was flat and soft. The pain in the region of the left kidney was increased on palpation. Neither kidney could be felt. The peripheral arteries showed a considerable degree of sclerosis. Temperature was 96 F., pulse 100, and of high tension. At 9 o'clock the patient was given ¼ grain of morphin hypodermatically. The pain did not decrease and the dose was repeated at 9:40 a. m. Severe pain persisted until 10 o'clock and then began slowly to subside. Purgatives and copious hot enemata were ordered.

October 7.—Patient had not urinated or had a bowel movement since the onset of the attack. The pain was now referred to as soreness. Vomiting and headache persisted. There was complete anorexia. Temperature, 96 F.; pulse, 90. About 1 dram of turbid urine was obtained by catheterization. This contained much albumin, no sugar, no red cells, a large number of pus cells, no casts.

October 8.—Temperature, 101 F. Patient was placed in the Presbyterian Hospital. Examination now showed evidences of myocardial involvement. There was positive venous pulsation in the neck, palpable tender liver, and edema of the bases of the lungs. Blood pressure registered 210 mm. At the suggestion of Dr. Sippy, 25 ounces of blood were withdrawn from the right arm, reducing the blood pressure one hour later to 190 mm. Croton oil, m. iii, and later m. v, was administered, but without result.

October 9.—Nine drams of urine were obtained by catheterization. This was distinctly sanguineous in appearance, contained much albumin, numerous pus cells, hemoglobin, but no casts and no red cells. Temperature ranged between 98 and 99 F. Leucocyte count was 16,500. In the afternoon marked arrhythmia developed. Patient was very restless, and complained of air hunger. On the evening of the same day, an exploratory operation was decided on and performed under nitrous oxid anesthesia by Dr. J. B. Murphy. The left kidney was brought into view and freely incised at the convex border down to the pelvis. The cut surface of the kidney was exceedingly dry, pale gray in color, and practically bloodless. No calculi were found either in the kidney, pelvis, or in the ureter.

October 11.—Anuria and constipation persisted. Patient was very restless and dyspneic, but still retained consciousness. Exitus took place the following morning, after six days of almost complete anuria.

Autopsy Findings.—Left kidney was normal in size, measuring 11.5 cm. by 5.5 cm., by 4 cm. Capsule stripped readily. The surface was markedly irregular, presenting numerous cicatricial depressions. The greater part of the organ was of a dull gray color with small areas of dark red. The cut surface was exceedingly dry, bloodless and firm in consistency. The middle portion of the organ presented a structureless whitish-gray area. This area was almost quadrilateral in shape and protruded slightly above the cut surface. It measured 7½ cm. in length and extended from the cortex to the pelvis. This enormous infarct, which occupied more than two-thirds of the entire organ, was sharply delineated on either side by a zone of intensely dark red tissue.

The renal artery and its larger branches were isolated and opened. The vessel walls were found thickened. The artery proper, just at its bifurcation, contained

an adherent red thrombus. This extended into the smaller branches and was continuous with the adherent white thrombi. That these continued into the smaller branches was demonstrated by sectioning the kidney. The right kidney was very small, measuring 7 cm. by 4 cm. by 2 cm., and markedly irregular. The upper third of the kidney was occupied by a large infarct, which had the same dull gray appearance and was sharply delineated from the rest of the kidney tissue. There were also small cortical infarcts. The pelvic fat was excessively developed, and involved the greater part of the organ. The right renal artery showed a still more pronounced thickening of its walls. At one point it presented a marked constriction, the lumen measuring not more than 1 mm. in diameter. The artery and its larger branches were plugged with adherent red and white thrombi.

Summary.—In this case, then, we are dealing with an arteriosclerotic individual, 44 years old, in whom no valvular lesion could be detected at any time. In the history of this patient we have to consider three distinct events manifestly dependent on a common cause: 1. Two years ago, gangrene of the left foot, preceded by severe cramp-like pains. This was soon followed by thrombosis of the vessels of the extremity with sepsis and metastatic foci in the lungs. At this stage there appeared albumin and casts in a previously normal urine, but no blood. 2. Eighteen months later the patient had two attacks of pain in the lumbar regions. Each attack was apoplectiform in onset and accompanied by the synchronous appearance of red cells and hemoglobin in the urine. 3. Two months later occurred a third attack, which was very much more severe and proved fatal. The pain was this time localized in the region of the left kidney. There was an almost total suppression of urine. The latter contained much albumin and hemoglobin. While it is deplorable that the heart could not be obtained for examination, I feel that we can safely rule it out as the cause. For, on the one hand, as was mentioned before, no symptoms of valvular disease were present. On the other hand, a ready explanation was furnished by the condition of the renal arteries. Thickening of the vessel wall and gradual narrowing of the lumen, with consequent slowing of the blood current, induced thrombus formation and its result, infarction. Undoubtedly the same process was responsible for the gangrene of the left foot.

Points of Special Interest in the Last Attack.—(1) Sudden onset. Pain at its acme from the onset and subsiding gradually. (2) Pain increased on palpation and deep breath. No radiation along the course of the ureter, nor toward the penis, scrotum, or thigh. (3) Almost complete anuria, the patient having passed not more than two ounces of urine in six days. (4) Absence of erythrocytes and casts in the sediment, marked albuminuria and presence of hemoglobin. (5) Constipation so obstinate that it could not be overcome by heroic doses of elaterin and of croton oil. (6) Absence of marked uremic symptoms.

GENERAL SYMPTOMATOLOGY.

As we have seen from the cases cited, the symptoms are not many nor are they constant. They can be best discussed under two headings: (1) Local symptoms, (2) accompanying or general symptoms.

Local symptoms are directly due to the infarction. These are pain and changes in the urine. Pain is the most important and constant sign. Three factors at least may contribute to the production of it: (1) Insult to the renal plexus; (2) perirenal inflammation or inflammatory reaction, and (3) tension on the kidney capsule. In most cases the pain is of great intensity and suggests renal calculus. It differs from the latter, however, in that it is not colicky, but is described by patients as stabbing or burning. Furthermore, it is not intermittent. The pain of renal infarct is at its acme from the onset, is continuous and subsides only gradually. It is increased by palpation, cough, deep breathing, change of posture; in other words, by movements of the affected organ. Schmidt, in his careful study of three cases, found that pain was somewhat relieved when patients lay on the affected side; in other words, by putting the kidney at rest. As to localization, this was in all cases in the region of the affected kidney. It is important to remember that the pain is confined to the kidney region proper and does not radiate along the course of the ureter or towards the genitalia.

With regard to urinary changes nothing pathognomonic was observed. Suppression of urine, which in mild cases may be followed by a transient polyuria, or total anuria, may take place. The latter was observed in cases of bilateral infarction. Albuminuria is the most common finding, and its appearance in previously normal urine, especially if associated with pain, is suggestive. Hemoglobin was the next most constant finding. Red cells were not as frequently found and then only in small numbers. Casts were absent in all but one case. Their absence may be due, as Schmidt suggested, to complete arrest of circulation in the affected area, the products of necrosis remaining *in situ*.

Accompanying or General Symptoms.—These are either due to the toxemia of renal insufficiency or are induced reflexly. The following were observed: Vomiting, collapse, severe headache, constipation, cardiovascular symptoms, in some cases leucocytosis and slight fever. Vomiting may be an early and a very distressing symptom. It is due, in Schmidt's opinion at least, to tension on the renal capsule rather than to uremic intoxication. The early onset and rather marked absence of other uremic symptoms seem to support his view. Cardiovascular phenomena are important because they point to a source of embolism and

suggest the possibility of infarct formation. According to Schmidt, high blood pressure speaks against an infarct. No observations on this point were made in the cases reported. In my case the blood pressure was 210 mm. and was but little affected by removal of 25 ounces of blood, a circumstance which casts suspicion on the above statement. Leucocytosis and slight elevation of temperature, observed in some of the cases, may be due to absorption of the necrotic renal tissue.

DIFFERENTIAL DIAGNOSIS.

It is hardly necessary to emphasize the difficulty, often impossibility, of recognizing the condition, even in the presence of marked symptoms. To quote Leube, "The diagnosis can rarely be made. The condition may be surmised with some probability when, in the presence of a possible source for the formation of emboli and infarcts, sudden pain develops in the region of the kidney, and albumin, blood or morphologic elements indicating nephritis appear in the urine."

In the diagnosis of renal infarct we must first exclude all conditions outside of the kidney and ureter capable of giving rise to sudden and severe abdominal pain. Among the most important are: gastralgia, perforative peritonitis, acute ileus, gallstones, embolism of the mesenteric artery, lead colic, and gastric crises. The consideration of the differential points in these conditions would take us too far from our subject, and, as they are, furthermore, familiar to every clinician, their discussion will be omitted here. In the second place, we must consider all conditions capable of giving rise to symptoms of renal colic or severe renal pain, such as (1) torsion of the ureter in a wandering kidney, (2) paroxysmal exacerbations of chronic nephritis, (3) calculus colic, (4) pseudocolic, which may be caused by (a) plugging of the ureter with tuberculous or neoplastic débris, blood clots, hydatids, (b) by obstruction due to catarrh of the ureteral mucosa, and (c) by functional spasm of the ureter.

It is important to decide first whether the pain is of renal or ureteral origin. The following conditions speak for renal origin: 1. Pain confined to kidney region proper. 2. Kidney tenderness. 3. Continuous character of the pain. 4. Albuminuria, casts, etc., in the sediment. The following point to ureteral origin: 1. Radiation of pain along the course of the ureter. 2. Tenderness in the course of the same. 3. Intermittent character of pain. 4. Presence of hydronephrosis.

Having established a renal cause of the pain, we still have to consider the following possibilities: (1) Twisting of the ureter of a wandering kidney; (2) acute exacerbation of chronic nephritis; (3) renal infarct. While the differentiation is not easy, the following points may be of value

as pointing to the diagnosis of infarct: (a) sudden onset of intense pain while the patient is at rest; (b) sudden appearance of albumin in the urine; (c) kidney tenderness; (d) presence of a valvular lesion of the left side of the heart.

Marked hematuria speaks against infarct and for nephritis, or malignant tumor. In the latter case, a palpable mass is frequently present at this stage. High blood pressure and marked uremic symptoms are more common in nephritis. Pain is never as severe in nephritis as it is in infarct.

In conclusion, it may be said that, while attention to the above symptoms may enable one occasionally to recognize a renal infarct in a marked case, the condition must still belong to the category of conditions best diagnosed postmortem.

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EFFECTS OF PROLONGED ADRENALIN MEDICATION ON THE HUMAN CIRCULATORY ORGANS.

WITH CASE REPORT.

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Adrenalin, once a drug of promise, is now in such general use and is employed in so many varying conditions, often with the greatest benefit, that it is important for us to learn all we can in regard to its deleterious effects on the human body. The work of Takamine, Cushny, Abel and many others has made us fully conversant with its physiologic action. Its value as a therapeutic agent no one can deny, though we, in common with many others, think that it is too generally administered, and in many instances without even a theoretic basis for its exhibition.

Physicians, and notably the resident physicians of hospitals, entertain very erroneous ideas as to the effects of the drug. Thus, it is generally supposed to cause a marked increase in blood pressure soon after its hypodermic administration. An injection controlled by a sphygmomanometer on the arm will, however, soon dispel this idea and demonstrate that in order to produce this condition adrenalin must either be thrown directly into the blood stream or given as an intramuscular injection, and that even then the elevation of the blood pressure is often slight and always very transitory. Increase of blood pressure is rarely produced when the drug is given subcutaneously, and in such instances the psychic effect of the injection should be taken into account.

Thus far the results of the drug in protracted, large or poisonous doses have been chiefly, if not exclusively, studied on animals, and those who have followed the work of Pearce, Adler, Loeb and numerous others can not fail to be impressed by the possible danger which may result from the persistent use of this powerful agent.

It has been definitely shown that in many but not in all instances the injection of adrenalin solutions into the circulation of animals causes lesions of a serious nature in the vessels. It has also been demonstrated that in many cases the degree of the lesion is not dependent on the size of the dose, nor yet on the relative body weight of the animals. Sometimes very minute amounts cause very serious changes, while at

other times very large doses produce no effect whatever. More recent communications show us that we have probably overestimated the effect of this drug in causing vascular lesions, since quite similar changes have also been reported in control animals. We have found from our experiments that an immunity is developed in animals as in most drugs of this class. This enables them to withstand very much larger doses than could previously be borne if the injections are continued for a long time. Thus, we now have a rabbit weighing 1800 gm. that outlives 50 drops, intravenously, of a 1:1000 solution.

As to the manner in which the lesions are produced, it was at first thought that the great elevation of the blood pressure which sometimes takes place on the administration of the drug caused an actual laceration of the walls of the vessels, a true mechanical lesion. In some cases this is true, but in most instances in which lesions occur it acts in some other way, causing the appearance of degenerative or necrotic foci, especially in the media of the vessels.

Attempts have been made to reproduce the changes which occur in human arteriosclerosis experimentally, and for a time it appeared that we could cause lesions like those seen in true arteriosclerosis. Further study has convinced us that the lesions produced by adrenalin in the vascular system of experiment animals are not those of true arteriosclerosis as seen in man. The interpretation of this discrepancy admits of at least two explanations; one, which now seems the more probable, is that adrenalin does not cause lesions in animals like those of arteriosclerosis in man; the other is that the tissues of the arterial wall react differently in animals than in man.

It, therefore, seems very important that we place on record the following case in which adrenalin was administered for over three years, the drug being given daily, intramuscularly, and in large amounts, varying from 10 to 120 minims per dose. Perhaps it is well, by way of justification, to state that our case was a most persistent one of bronchial asthma in which anything which would give even momentary relief was justifiable.

History.—Mrs. M., 35 years old, houseworker, born in Austria; thirteen years in the United States. Admitted May, 1904, and died in April, 1907. Family and personal history was negative, except for one miscarriage at the third pregnancy. No specific history; no neurotic disposition, except for worry and excitement brought on by marital troubles.

Present Illness.—Began in December, 1901, with a severe cough, the result of a cold contracted while exposed to rain and snow. This cough continued, accompanied by dyspnea, until 1904, when the condition became unbearable. Various drugs that were tried proved of no avail.

Status Præsens.—Neck short, muscles stand out prominently, especially with inspiration. Patient has anxious look, breathes through the mouth, gasping for breath. Examination of nose disclosed the presence of about ten small polypi. Heart: Apical impulse not visible; heart impulse not felt. Very difficult to make out cardiac dulness. Auscultatory percussion gives normal cardiac outline. Sounds normal at all ostia. Pulse, 90 per minute, regular, equal, fair tension, vessel wall moderately thickened. Blood pressure: Systolic, 130; diastolic, 85. Lungs: Expiratory period very much prolonged. Mouth breather. On palpation, here and there fremitus with inspiration and expiration. Percussion: Right anterior, below clavicles, resonance is impaired, rest of lung wooden. Auscultation: Inspiration short, harsh, stopping suddenly, followed by a long expiratory period which is accompanied by wheezing, whistling, and moaning sounds. The breathing can be heard at a distance from the patient. Respirations, 17 per minute.

Treatment.—Although various other methods of treatment were instituted, including the removal of the polypi, only the adrenalin medication will be detailed here. The drug was used intramuscularly in 1 to 1000 solution; its effects observed, and if no relief followed, another injection was given. As a rule, one syringeful was enough to cut short an attack; occasionally, however, even two injections would not suffice, and there are records showing the exhibition of as much as 120 minims of the drug. The dosage varied with the severity of the attacks. It was possible to curtail some seizures with 10 minims. The long time of the patient's stay in the hospital gave ample opportunity for observing the effects of adrenalin chlorid on the circulatory system, and the observations on this system only will be given here. Its effects, as far as the attacks are concerned, can be stated in a few words: All symptoms of an asthmatic attack were relieved. The pulse could often be felt more distinctly after using the adrenalin than before, whereas, during the asthmatic attack it was barely perceptible. A few minutes after the administration of the drug, the arterial pressure as observed during one of the attacks rose and remained elevated for about ten minutes. A reading was as follows: Systolic pressure, 120; diastolic pressure, 85. After the injection of 20 minims of adrenalin, the pressure was again ascertained without removing the cuff from the arm and gave the following results: Systolic pressure, 145; diastolic pressure, 100. The numerous repetitions of the injections—the patient having received during her three years' stay in the hospital no less than 2,000—did not permanently alter the blood pressure, as readings shortly before death show that the pressure remained at about the same level during both free and seizure periods; in fact, one could not tell from a clinical examination shortly before death that the heart and vascular system had sustained permanent injury from the enormous quantity of adrenalin chlorid injected during these three years. If we allow only 10 minims to a dose (the smallest injected), the total amount of the drug given was 44 ounces.

Summary of Autopsy Findings.—Inspection: Adult woman. Moderate cyanosis of the skin. Purpuric blotches over entire surface, varicosities over calves. Face congested, pupils dilated, neck and lips swollen. Slight anterior kyphosis of spinal column. Abdomen distended. Section: Muscles deep red, natural. Panniculus deeply colored, abundant. Veins widely dilated, arteries large, thickened. Mammæ well developed. Precordium covered by emphysematous borders of lung. Pleura and pericardium negative. Heart small, right ventricle collapsed, empty. Left ventricle contracted, empty. Aortic segments slightly thickened; marked cupping of sinuses and funnel-shaped extension into coronaries; other valves normal. Heart muscle soft, turbid, friable, moderate quantity of epicardial fat, right auricle shows great distension. No thickening of endocardium. Coronary arteries markedly thickened, not calcified. Weight

of heart, 8 ounces. Hypertrophy of adenoids of tongue and pharynx, all neck structures edematous, including folds of larynx. Thyroid large, natural; no thymus. Lymph nodes of neck enlarged, anthracotic; show healed tubercles. The right innominate and subclavian arteries at their origin from the arch show slight dilation. The left carotid shows slight spindle-shaped dilation in mid-portion. Dilated arteries show roughening of intima and aorta somewhat irregularly thickened. Small trunks of neck show slight atheroma. The larynx and large bronchi contain tenacious mucus; mucous membrane atrophic. Mucous membrane of medium sized and small bronchi congested. Mucoid spirals abundant in finer air pasages. Lungs show emphysema, edema and congestion of posterior portion. Pulmonary vessels show no change. Peribronchial lymph nodes show anthracosis and healed tuberculosis. Liver large; a few isolated areas of necrosis. Gall bladder and ducts negative. Spleen, enlarged, deep purple and soft. Stomach, negative. Small and large intestine negative. Appendix negative. Mesenteric lymph nodes show calcification and necrosis, old. Tissues about pancreas show chronic inflammation and old areas of fat necrosis. Pancreas, deep purple in color, infiltrated in every direction by recent hemorrhage; marked arteriosclerosis of pancreatic vessels, especially of pancreatica magna, but no rupture present. Adrenal bodies large; no gross abnormality. Kidneys, congestion and edema; arterial thickening; parenchymatous degeneration; moderate interstitial nephritis. Internal genitals, negative. Bladder, negative. Aorta and large trunks of abdomen and pelvis present a moderate diffuse thickening with occasional minute areas of atheroma without calcification in the intima. Brain, moderate edema of membranes; vessels at base show slight thickening; otherwise negative.

Anatomical Diagnosis.—Bronchial asthma, terminating with pancreatitis hemorrhagica, complicated by parenchymatous nephritis, pulmonary edema and congestion.

Microscopic Examination.—Brain and medulla: Corpora amylacea in considerable numbers beneath membrane, notably along floor of fourth ventricle. Congestion of minute vessels and occasional slight hemorrhages by diapedesis. Occasional ganglion cells show atrophic changes.

Lung: Congestion in posterior portion, marked emphysema. Smaller bronchi surrounded by inflammatory thickening and tubes filled by compact mucus in the meshes of which are many eosinophilic leucocytes. Large vessels show moderate subendothelial hyperplasia and occasional hyaline degeneration of media.

Liver: Parenchyma show pronounced albuminous degeneration, with moderate fatty infiltration. Slight brown atrophy, with ferruginous pigmentation in places. Supposed necrotic areas show beginning fibroid replacement of parenchyma, general edema. Blood vessels negative.

Pancreas: Recent extensive areas of capillary hemorrhage, considerable quantities of old iron pigment, probably representing old areas of hemorrhage, extensive necrosis of parenchyma, both in acini and in bodies of Langerhans. Extensive necrosis of pancreatic ducts. No changes in the interstitial tissue.

Kidneys: Extreme acute parenchymatous degeneration with extensive desquamation of tubercular epithelium. Hyperemia of vessels, with hemorrhage by diapedesis. Hyaline degeneration in small foci in media and subendothelial areas.

Spleen: Congested lymphoid hyperplasia. Hyaline degeneration affecting media of many blood vessels.

Lymphnodes: Lymphoid hyperplasia of moderate degree. Healed tuberculosis in bronchial nodes. Hyperplasia of lymphatic endothelium and general anthracosis. No vascular lesions noted.

Uterus: Endometrium thickened. Marked proliferation of subendothelial layer and of adventitia and of most blood vessels; no changes of media.

Ovary: Vascular changes as found in uterus, otherwise tissue is normal.

Thyroid gland: Entirely normal, but shows evidence of excessive activity.

Adrenal glands: Pronounced fatty infiltration of cortex. General hyperplasia of cells in medulla, particularly of those bordering on the large venous sinuses. Marked congestion of blood vessels in medulla.

Heart: Considerable quantity of epicardial fat with infiltration of stroma. Marked capillary hyperemia. Marked brown atrophy with fatty degeneration and acute parenchymatous degeneration. Many atypical karyokinetic figures in the nuclei of muscle cells. The coronary vessels show marked thickening of subendothelial layer, with marked hyaline degeneration of both the muscle cells and the hyperplastic connective tissue. Occasional circular foci of necrosis in media and subendothelial tissue.

Aorta: Endothelial layer broken and eroded in many places. Occasional areas of endothelial hyperplasia. Minute areas of necrosis, oval or spherical in shape, chiefly in subendothelial layer, and involving both white fibers and yellow elastic, as well as the muscle fibers. In a few areas very slight calcareous infiltration is demonstrable, but fatty disintegration can not be shown. No distinctly evident lesions in vasa vasorum.

Main trunks (femorals and carotids): The nodular subendothelial thickening and necrosis is very marked in trunks of this class, and in most of them the internal elastic layer is broken in many places. The necrotic process in the media is also much more marked than in either the larger or the smaller trunks. The vasa vasorum show no very apparent changes.

Small trunks: Some of these vessels show marked hyaline degeneration, with resulting necrosis in the media, the foci of subendothelial necrosis mentioned in the other vessels is not present.

The visceral alterations are predominatingly of an acute parenchymatous type and are apparently of recent origin for the greater part. Some of the organs, notably the liver, heart and lungs, show also the changes resulting from chronic passive congestion, probably of considerable standing. The lungs show, in addition, the typical changes of a chronic bronchial asthma. The pancreatic lesion apparently originated some weeks before death, finally terminating with an acute diffuse capillary hemorrhage and resulting necrosis. It does not appear probable that these changes in the pancreas are to be directly attributed to the long continued use of adrenalin, although this explanation is to be considered. The alterations in the medulla of the adrenalin bodies may be etiologically related to the adrenalin medication.

The most striking lesion found in the aorta and large trunks is preeminently a type of focal necrosis, which we believe to have been entirely separate and distinct from the ordinary changes of arteriosclerosis which are also manifested in lesser degree in the same vessels, and which are probably due to the asthma *per se*. This focal necrosis, and especially that involving the media, is quite similar to that produced in experi-

mental adrenalin poisoning, and we believe it to be due to the prolonged and free administration of this drug in this particular case.

While admitting that the necrotic changes in this case were due to the adrenalin medication, we do not believe that they are in any sense to be taken as contraindicating a moderate and temporary utilization of adrenalin in appropriate cases. On the contrary, we believe that the relatively slight degree of these changes in a case in which the drug was used so freely and for so long a time indicates that in ordinary cases it may be used with relative impunity in amounts sufficient to produce therapeutic results.

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METABOLISM EXPERIMENTS IN ARTIFICIAL NUTRITION,

WITH SPECIAL REFERENCE TO THE HYPODERMIC METHOD.

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The whole subject of artificial nutrition presents great fascination for internists both from the theoretical and the practical point of view; for the idea of nourishing the body, meeting its physiologic needs, so to speak, without the knowledge or consent of the patient, when occasion arises, has seemed an end highly desirable at times.

The conditions under which this would be of value are, of course, various, and need not be discussed here beyond pointing out the fact that in cases of subnutrition which, in part or whole, preclude the natural method of maintaining the physical economy, some such method would often be of the greatest use. Thus, it is indicated in acute gastroenteritis in children, in marasmus, in strictures of the alimentary tract when the patient comes under observation in a condition too weakened to allow of an operation for the time being, etc.

With the introduction of the stomach tube in 1870, by Kussmaul, we were enabled to nourish certain cases in which forced feeding is a necessity, despite the existence of a fairly normal digestive tract, as in cases of mental disease. Later, the rectum as an auxiliary stomach came into general use. Attempts were made to give nourishment by means of hypodermic food solution, or by the intraperitoneal route. Of course, any form of artificial feeding, to be entirely sufficient, has to meet the actual needs of metabolism. The requisite amount of nitrogen and heat units must be furnished or the organism will be forced to run at an economic loss, resulting in loss of flesh and strength.

Our knowledge of these requirements has been greatly increased since Voit and his pupils determined the average amount of the different food elements used by individuals doing light or heavy muscular work and maintaining their body weight. According to this standard, a person of average weight (70 to 75 kilos) needs about 118 grams of protein, 56 grams of fat and 500 grams of carbohydrate, with a total fuel value of 3.000 large calories, although Voit[1] was able to establish nitrogenous

1. Voit: Ztschr. f. Biol., xxv, 261.

equilibrium for a short time in one patient who took only 8 grams of nitrogen, which corresponds to 48.5 grams of proteid, for a day's ration. This, however, he considered far too small an amount to maintain nitrogen equilibrium for any length of time.

Chittenden[2] became convinced that a low protein diet could be maintained, not only without detriment to the individual, but to his actual advantage, provided sufficient heat units were furnished by the other food elements. This he proved to his satisfaction in his interesting experiments on athletes, soldiers and students, representing individuals doing, respectively, severe, moderate or light muscular work. He found that the average requirements per kilo of body weight were as follows: 0.12 gram nitrogen, representing 0.65 gram protein per kilo of body weight, with a total fuel value of the food represented by 32 calories per kilo, made up largely of fats and carbohydrates.

This, therefore, can be taken as representing the minimum food requirements necessary to maintain not only the nitrogenous equilibrium, but the general physical condition and body weight of persons who are at work, while at rest the calorific value of the food can be reduced to about 25 calories per kilo.[3] Any form of alimentation to be complete must meet these requirements, although under pathologic conditions one would be satisfied with something less than the ideal.

With the older standards, the problem seemed out of reach, but with the introduction of these lesser requirements artificial nutrition seems a much more promising field, and it was with this in mind that the following studies were undertaken.

In approaching this subject, two questions naturally present themselves: (1) Is the method ordinarily in use capable of accomplishing satisfactory artificial nutrition? (2) If not, wherein does it fail, and what other methods offer a possible solution of the difficulty?

In rectal feeding, the most common method of artificial nutrition, we have these questions to answer. As to whether this form of feeding is capable of supplying the needs of metabolism, if one regularly weighs these patients daily or even watches them clinically from day to day, the answer must be, No. They do not thrive. This, I think, will be borne out by the clinical experience of most of us. Rectal feeding is, at best, a poor substitute for stomach feeding, although, of course, patients differ, and in some it seems more successful than in others. It must be borne in mind, however, that most people can go without food very

2. Chittenden: Physiologic Economy in Nutrition.
3. Lusk: Jour. Am. Med. Assn., xlix, 201.

comfortably for a number of days, provided they are supplied with water, but after a certain time, whether on rectal feeding or not, they often seem to retrograde suddenly.

In order to answer the question as to the specific cause of failure in most of these cases, one must study the metabolism and carefully estimate the intake and output, with especial reference to the nitrogen, as the best index of metabolism. The following figures show the results of metabolism in three cases of rectal feeding and may be taken as fairly typical of a large class, as they occurred in one of the large city hospitals, under nursing conditions which are as good as can be found. If these results are true under favorable conditions, what can be expected under ordinary conditions, outside the hospitals?

It can not be said that more satisfactory results may not at times be obtained by rectal feeding. But these cases probably represent the average. In all of them the usual precautions were taken: the colon was cleared daily, the injections were given high up, and the report, in every instance, was that they were "well retained." The entire twenty-four-hour urine, all results of rectal irrigation, and all stools were saved, and, together with a sample of the food, were sent to the laboratory daily. It seemed a work of supererogation to estimate the intake and output of nitrogen, for the results of the cleansing enemata were evidently an almost clear return of the nutrient material, and one could tell by inspection that little, if anything, was being absorbed. The following figures, however, represent the daily nitrogenous balances, estimated by the Kjeldahl method, and show graphically the failure of this method of nutrition; since in these cases at least nitrogenous equilibrium was far from being maintained.

CASE 1.—*Gastric Ulcer.* Man, aged 46, weight 115 pounds.

History.—Patient had been on rectal feeding three days before the test was begun. The nutrient fluid consisted of peptonized milk and eggs, 1240 c.c. per twenty-four hours, with a total nitrogen value of 11.78 grams.

NITROGENOUS BALANCE.—FIRST DAY.

Total intake of food nitrogen	11.78 grams.
Total nitrogen output (urine, 4.74 grams; feces, 23.95 grams)	28.69 grams.
Total loss of nitrogen, 24 hours, output in excess of intake	16.91 grams.
Total loss in body weight	1 pound.

NITROGENOUS BALANCE.—SECOND DAY.

Total intake of food nitrogen	12.40 grams.
Total nitrogen output (urine, 11.5 grams; feces, —; irrigation, 22.72 grams)	34.22 grams.
Total loss of nitrogen, 24 hours, output in excess of intake	21.80 grams.
Total loss in body weight	2 pounds.

NITROGENOUS BALANCE.—THIRD DAY.

Food formula changed this day to peptonized milk, glucose and water, 2,000 c.c. in all for the twenty-four hours.

Total intake of food nitrogen..... 7.20 grams.
Total nitrogen output (urine, 9.58 grams; feces, 6.43 grams) .....16.01 grams.
Total loss of nitrogen, 24 hours, output in excess of intake... 8.81 grams.
Total loss in body weight ..... 2 pounds.

In this balance for the third day we see for the first time that something was actually absorbed by the rectum, or else retained, for the food intake was 7.2 grams nitrogen, and the fecal nitrogen equals 6.43 grams, leaving an absorption balance of + 0.67 gram nitrogen, which is, of course, so small as to amount to nothing from the standpoint of nutrition.

(NOTE.—The probable explanation of the fact that on the first two days the nitrogen in the stools and irrigations was greatly in excess of that artificially injected in the enemata is that material from previous days was retained and expelled along with the stools passed on test days.)

CASE 2.—*Gastric ulcer.* Man, aged 27.

Food: Peptonized milk and eggs.

NITROGENOUS BALANCE.—FIRST DAY.

Total intake of food nitrogen ..... 6.37 grams.
Total nitrogen output (urine, 15.52 grams; feces, —; irrigation, 6.89 grams) .....22.41 grams.
Total loss of nitrogen, 24 hours, output in excess of intake...16.04 grams.
(Patient could not be weighed.)

NITROGENOUS BALANCE.—SECOND DAY.

Total intake of food nitrogen ..... 6.35 grams.
Total nitrogen output (urine, 15.60 grams; feces, 9.06 grams) .....24.66 grams.
Total loss of nitrogen, 24 hours, output in excess of intake...18.31 grams.

CASE 3.—*Postoperative perforating gastric ulcer.* Man, aged 23.

Food formula, peptonized milk and egg, with panopeptone. Patient had been on this several days, when test was made only on one day, so that it is rather incomplete. Daily volume, 712 c.c.

Total intake of food nitrogen ..... 4.69 grams.
Total nitrogen output (urine, 19.04 grams; feces, 9.84 grams) .....28.88 grams.
Total loss of nitrogen, 24 hours, output in excess of intake...24.19 grams.

Little comment is needed in addition to a glance at the figures presented to prove the inadequacy of rectal feeding in these cases, and it may be assumed that in the vast majority of cases the results are little, if any, better.

The minus nitrogen balance varies from — 8.81 grams to — 24.19 grams, and is accompanied by a steady loss of weight in the first case (the only one weighed), apparently also in the others.

In a review of the literature on this subject, the only paper found to approach it from the standpoint of exact metabolism was by Edsall and Miller,[4] who investigated two cases with rather better results, so far as

4. Wisconsin Med. Jour., 1903, i, 87.

concerned actual absorption of the nutrient mixture of peptonized milk and eggs by the intestinal wall, but the nitrogenous loss averaged 11.8 to 70.9 grams nitrogen for the test period of six days. From clinical observation, however, and from the foregoing cases, the conclusion may be drawn with considerable certainty that rectal alimentation, as ordinarily practiced, is of little or no value in most instances, while in some it may prove harmful by using up the patient's strength. Of course, it has been proved that water is well absorbed by the rectum and that this method of introducing water is of extreme value.

Having satisfied ourselves of the foregoing facts, the next question which naturally arises is: Can nutritive equilibrium be maintained more satisfactorily by any other artificial means?

Many investigations have been undertaken to determine the effect of intravenous injections of various foodstuffs in solution. Although the prime object of most of such attempts has been to study the effects of these substances on the organism, incidentally side lights have been thrown on the subject of nutrition, although mostly in a negative way, as substances so injected have been proved unsuitable for use in artificial nutrition, either because of their toxicity or because they are immediately excreted for the most part.

Leaving out of consideration intraperitoneal nutrition as unsuitable and impracticable for continued use, one naturally turns to the problem of artificial nutrition by the hypodermic injections of foodstuffs. With the introduction of Chittenden's lowered food requirements it occurred to the writer to attempt to prepare an artificial, soluble food, containing the precise nutritive requirements for an individual calculated on Chittenden's figures; to inject it into the subcutaneous tissue and determine the nitrogen balance day by day, to see if the requirements of the body were being met, and the body maintained, not only in nitrogenous equilibrium, but also in weight.

The literature on this subject is surprisingly scanty. There are no articles accessible to the writer in which the subject has been approached from the standpoint of metabolism. What has been done may roughly be divided into clinical inquiries and laboratory experimentation. The clinical observations have been of the crudest sort, and the reports contain almost no data concerning the cases or, at best, very insufficient data. Whittaker,[5] in 1877, reported the case of a man nourished for six days by subcutaneous injections of milk, extract of beef and later cod liver oil; but from the article there is no proof that the man was nourished

5. Am. Jour. Med. Sc., April, 1877.

in the real sense of the word, for no mention is made of body weight during this period, of the total amount of food injected, nor of the excretions, and we know that a patient can survive a short period of starvation with comparative ease. Kreng[6] injected 15 to 20 c.c. of olive oil hypodermically for twenty days and succeeded in maintaining the patient's weight (?) and strength.

Pick[7] quotes a case from Whittaker, who nourished a girl suffering from gastric ulcer, with a weak pulse and high temperature, for four days by hypodermic injections of milk and beef-blood, with "great increase in weight and strength, after which period the patient was able to take nourishment by mouth and the temperature fell." The dose of milk was a dram at a time, which is an absurdly small amount relative to the nutritional requirements, and makes one extremely skeptical of the results as recorded.

Leube[8] injected a 20 per cent. sugar solution and found that it was well borne if only a few cubic centimeters were given at a time, but the limit of absorption was 15 to 20 grams of sugar in the twenty-four hours, all beyond this being excreted in the urine.

A more recent report by Barker[9] speaks of the successful use of a 5 per cent. glucose solution in normal salt solution; this gives a solution which has the same freezing point as normal blood, — 0.56° C. He used it in preparing some patients for operation, and only in one instance were the injections followed by glycosuria, although he fails to state the amounts injected, and gives no weights or metabolism data. This was tried on one case of marked asthenia from pyloric stenosis, but without success, as the patient died of exhaustion. On the other hand, most other experimenters agree that the usefulness of glucose is very slight, as it is so promptly excreted when given in nourishing amounts, while in the hands of some it has caused necrosis at the point of injection.

Turning to the purely experimental aspect of the subject, we find more data, but the results have been largely negative or unsatisfactory.

Of the substances tried, fat, in the form of oil or butter, has been most frequently used. Without going into the details of the various experiments, we may take Henderson and Crofutt's[10] statement as embodying the latest and most satisfactory results of experimentation along this line. They say: "Oil injected subcutaneously is readily and widely distributed through the subcutaneous tissue. It is not transformed *in*

6. New York Med. Jour., March, 1876.
7. Deutsch. med. Wchnschr., 1879, v, 31.
8. Verhandl. Cong. innere med., Wiesbaden, 1895, xiii, 418.
9. Am. Med., 1905, ix, 234.
10. Am. Jour. Physiol., 1905, xiv, 193.

situ into adipose tissue. The tissues react to its presence as to any non-irritating, foreign substance. In the blood and lymph it does not appear in detectable amounts, and, while the oil is ultimately absorbed and utilized in metabolism, the process is one of extreme slowness. Oil injections in any moderate amount are, therefore, practically without nutritive value."

Winternitz[11] found that only 2 to 5 grams per day were utilized and that for subcutaneous nourishment it was not of practical value.

When we come to consider the availability of protein for subcutaneous injection, we are met by a variety of opinions. Eichorn,[12] in a series of experiments, used cow's milk (1/3 water), "Sanders peptone" and egg albumin. He concluded (1) that they are wholly absorbed, (2) that egg albumin often leads to abscess formation, (3) that cow's milk, diluted, takes the longest time for absorption, (4) that there is no local reaction from 20 grams of peptone. He also injected five dogs with albumin, olive oil, cod liver oil, almond oil and sugar solution, and states that most of the dogs maintained their weight. Few details of the experiments are given and there are absolutely no metabolism figures; the whole subject is very incompletely treated.

In another series of experiments, he used defibrinated pigs' blood and calves' blood, but without satisfactory results, and concluded his article by saying: "When we look at the results of subcutaneous injection of foods, we can assume that materials which do not inflame the cellular tissue when injected can be used for a while, often to advantage, to save life or postpone death by starvation."

Leube[13] found that the injection of 18 grams of "somatose" into a dog caused marked disturbance of well-being and led to albuminuria, due to renal irritation (see also results of somatose injections in these experiments).

Ewald,[14] discussing the subject, dismisses with a word albumoses and peptones as poisonous and useless.

Leube,[15] in a later article, speaks much in the same way, but suggests that possibly albumin, in the form of an alkali albuminate or syntonin, might be of use, although he had not tried it (see second experiment in this series).

11. Winternitz, Ztschr. f. klin. Med., 1903, l, 80, 101.
12. Wien. klin. Wchnschr., 1881, 918.
13. Verhandl. Cong. innere Med., Wiesbaden, 1895, xiii, 418.
14. Cong. internat. de méd., xiii, Paris, 1900.
15. Ibid.

Four years ago Trolldenier[16] used an albuminous substance intermediate between the peptones and albumoses. Of this he gave 100 c.c. (10 per cent. solution) to each of several dogs. In summarizing his results he says that the dogs maintained their weight; that the urine showed albumose; that the injections were painful, and that abscesses developed at the point of injection. It is hard to believe that these dogs could possibly have kept their weight on the amount of protein which Trolldenier gave them, as it has been found that a dog needs at least 0.3 gram nitrogen per kilo to maintain nitrogenous equilibrium, while these dogs received but a fraction of that, about 0.2 gram.

From this brief review of some of the most important contributions to the subject, it can readily be seen that the problem of providing sufficient food to an animal by injection and at the same time approximately maintaining its nitrogenous equilibrium, to say nothing of its weight, is a most difficult one. It was felt, however, that it would be exceedingly desirable to attempt it, inasmuch as, if successful, some plan might be evolved for artificial nutrition in man, although any method to accomplish this successfully must be both clinically safe and nutritively sufficient, or nearly so, and must rest on the scientific facts of metabolism. Toward this end the following experiments were performed on dogs:

EXPERIMENTS ON DOGS.

Preparation of the Dogs.—As a routine, the dogs were put on the regular laboratory diet and confined in metabolism cages, where all excreta could be saved for analysis. As a rule, the dogs lost a little weight for a few days, and then settled down to almost constant weight from day to day. It was not until this had been accomplished that an experiment was attempted.

In the first attempt a food which was theoretically perfect was prepared from "somatose," representing the protein element in the form of soluble meat peptone, at the dog requirement of 0.3 gram nitrogen per kilo; the remaining requisite number of heat units (on human basis) being made up of glucose in normal salt solution, the whole being sterilized by thorough boiling.

EXPERIMENT 1.—Three preliminary injections were made of this food, the first representing 0.66 gram somatose per kilo, the other two 0.42 gram per kilo each, and the effects were noted. The larger amounts caused marked toxic symptoms, trembling, inability to stand, and rise of temperature, a trifle over 4° F. within four hours. The smaller amounts were better borne, but still gave rise to some toxemia. The urine after the third injection gave a positive biuret reaction, and sugar was also present, but apparently in small amount. After a few days of rest on regular mouth-feeding, a forty-eight hour period was begun with the same food, dividing the twenty-four hour requirement into three injections for morning, afternoon and evening; at each injection an amount of peptone was used equal to 0.5 gram per kilo of weight.

Without going into the details of this experiment, it was seen that the dog showed less and less reaction, although the effects were too severe to constitute a result at all satisfactory from a clinical point of view. The temperature rose

16. Berl. klin. Wchnschr., 1903, xl, 912.

from 2° to 3° F., and the dog became weak and ill. the urine was less red in amount, contained albumin, peptone, sugar, hyaline and granular casts. The injection fluid collected on the under side of the body and caused marked edema. Between the 10 p. m. and the 10 a. m. feeding of the following day, the dog largely recovered its normal physical condition.

Following the period of injections, the dog passed an excessive amount of urine, probably from the subsidence of the edema, and continued losing some weight, even after it had been on regular mouth feeding again, receiving daily the same amount of food that had maintained it previously at a practically stationary weight. This loss in weight continued for a few days, then the weight remained stationary at a lower level. This, curiously enough, was the rule after most of the injection experiments. These results were not such as were thought worth following up as the toxemia was too marked, and for this reason chemical analyses were not made. Table 1 shows in graphic form the data collected.

TABLE 1.

	Date.	Weight. kilos.	Food Solution. c.c.	Volume Urine. c.c.	Urine. Sp. Gr.	Clinical Notes.
1.	March 30.....	6.43	†	340	1016	Dog well.
2.*	March 31.....	6.66	315	138	1045	Dog weak; some difficulty in standing. Temperature 104.5° F. Edema.
3.*	April 1.....	6.70	315	160	1043	Has had six injections; condition about same; urine contains albumin, peptone, sugar, hyaline and granular casts.
4.	April 2.....	6.03	†	705	1011	Dog fairly well again.
5.	April 3.....	5.86	†	390	1014	Urine: albumin, distinct trace; sugar absent, occasional cast.

* Injection period. † Regular food.

EXPERIMENT 2.—In the second experiment it was thought that possibly an alkali albuminate made from meat would meet the essential qualities of solubility and being capable of sterilization and might also be found to be less toxic than the peptone; this was prepared and diluted with normal salt solution. No account was taken in this experiment of furnishing the required calories, as it was undertaken solely with the view of seeing whether or not such a preparation would be of use.

The results of the injection of the alkali albuminate were most unsatisfactory, causing vomiting, bloody diarrhea, renal irritation, and local necrosis at points of injection.

The meat peptone and albuminate having proved so unsatisfactory, it was thought that possibly the peptone from cow's milk might be better borne, for it was conceivable that some of the toxicity of the meat peptone preparations might have been due to the extractives present.

In order to make this milk peptone, the certified city milk was used, after removing the gravity cream (as we have seen the fats are so slowly and insufficiently absorbed); this was then digested for three hours, by means of dry extract of pancreas with dilute sodium carbonate. The liquid was then sterilized by boiling, strained and put in sterile flasks after removing a sample for nitrogen determination.

EXPERIMENT 3.—For this experiment a small, pregnant dog, weighing 5.19 kilos, was used, and in order to find out at once the toxicity of this milk peptone, rather large amounts were used, equivalent to 0.4 gram nitrogen per kilo, divided into two doses, given twelve hours apart. Following the first injection, the dog gave birth to one normal pup. There were only moderate toxic symptoms, nothing

like as severe as those following beef peptone and albuminate. Although the results with the milk peptone were not entirely satisfactory, it was decided to go ahead, employing a three-day period with this large amount of protein injection. The reason for using so much more than the absolute dog requirement was to determine whether or not it was dangerously toxic, this percentage of nitrogen per kilo being nearly four times that required for man.

In spite of this, it will be seen that the mother lost weight decidedly, and after the first day the temperature rose 2° F. and remained up. Some milk was secreted, but the pup failed to get sufficient nourishment and lost weight steadily. At the end of the third day, the mother was only in fair condition, was considerably poisoned, as evidenced by temperature, malaise and suffusion of conjunctivæ. The pup had lost in weight and strength, so it was decided to stop the experiment and return the mother to regular mouth feeding. This was done at the end of the third day, and, although more milk began to be secreted, the pup was now too weak to get a supply, and died on the fifth day. After the first day, the mother refused all water by mouth, as she was evidently receiving sufficient fluid from the injections.

It will be seen on examining Table 2 from this case, that at the end of the first twenty-four hours, the amount of urine excreted was smaller than normal (the usual occurrence in these cases), but of very high specific gravity, 1076 the first day and 1052 the second. These figures were much higher than any obtained throughout the entire series of experiments, and although no exact metabolism experiments were made, as the case was of too short duration and the conditions too exceptional to make it of value, the rate of metabolism was evidently excessive and was unquestionably a great factor in the safety of the animal, for the next two dogs, in one instance on the same and in the other on a smaller amount of nitrogen per kilo, died of toxemia.

In trying to find a satisfactory explanation for this fact, viz., that this dog survived these injections, it was learned that Zachwegrwski[17] proved that in pregnant women there was antepartum nitrogen retention, and that postpartum there was a decided nitrogen loss, equilibrium not being established for four or five days, or even longer. He believed that the involution of the uterus caused the high nitrogen output accompanied by excessive nitrogen metabolism. It would certainly seem that this was the case, as the animal lost flesh out of proportion to the other animals, although it was on a higher percentage of nitrogen. So far as the pup is concerned, the method of hypodermic feeding of the mother failed to furnish the requisite amount of food, but as this was a very severe test for an artificial form of feeding, it is not surprising that it failed to meet these unusual demands.

TABLE 2.

	Date	Weight kilos.	Volume Urine. c.c.	Urine. Sp. Gr.	Food.	Clinical Notes.
1.	July 29.....	5.21	215	1020	Regular	Well and lively.
2.	July 30.....	5.14	295	1012	Regular	
3.	July 31.....	5.19	135	1020	Regular	
4.*	Aug. 1.....	5.12	115	1076	0.4 gr. N. per k. in peptonized milk.	Dog vomited. Rather weak; gave birth to pup. Weight of pup 21 grams.
5.*	Aug. 2.....	5.03	295	1052	"	Dog still weak. Pup weight, 18 grams.
6.*	Aug. 3.....	4.90	365	1031	"	Dog still weak. Pup weight, 17 grams.
7.	Aug. 4.....	4.38	515	1011	Regular	Dog better. Pup weaker; 16 grams.
8.	Aug. 5.....	4.40	210	1020	Regular	Pup weaker; 15 grams. (Died next day.)

* Injection periods.

17. Ztschr. f. Biol., 1894, xxx, 405.

EXPERIMENT 4.—In order to see whether the peptonized milk would prove as toxic under what might be termed normal conditions, another dog was injected with the same amount of nitrogen per kilo, namely 0.4 gram, divided into two doses daily. After the first injection, the toxic symptoms of the peptone were very evident, for the dog looked sick and could not rise. It received only three injections, at twelve hour intervals, showing after each more and more evidence of toxemia and dying twelve hours after the third injection.

The autopsy showed marked subcutaneous edema on the flanks and under the belly; skin dark purple and ecchymotic. On section, this area of edema was found infiltrated with bloody, serous fluid. The organs were sent to the Cornell Pathologic Laboratory and the following report was received:

"*Liver.*—The whole section stains poorly. Many lobules show a marked degeneration as from a severe toxemia. The ability of the cell body and nucleus to take on basic stain has been lost, indicating changes in the direction of degeneration, if not necrosis. The vascular elements seem normal.

"*Kidney.*—Tubules were in a condition of cloudy swelling and granular degeneration. Glomeruli, interstitial tissue, blood vessels appear normal.

"*Heart and Spleen.*—Normal.

"*Intestines.*—Some congestion in spots; no hemorrhages."

EXPERIMENT 5.—The next trial to be recorded was with the peptonized skimmed milk, but peptonized only one hour and a half, as it was thought that possibly the length of the peptonization might make some difference in the degree of toxicity. Then instead of suddenly changing from all mouth feeding to all hypodermic feeding it was thought that it might be safer to make the change more gradually. The first day, three-quarters of the regular amount were given by mouth and one-quarter by hypodermic injection. The next day half mouth feeding and half hypodermic injection were resorted to, always on the basis of 0.3 gram nitrogen per kilo.

These injections caused some toxemia from the first, but it was not until the second day that the dog looked really ill, and on the morning of the third day he was found dead, apparently from the same form of toxemia as killed the preceding dog. The first day's injection represented 0.075 gram of nitrogen per kilo; the second day's, 0.15 gram of nitrogen per kilo.

The autopsy revealed local edema with serous bloody fluid. The examination of liver and kidneys could not be completed in time, but on gross examination presented only slight evidences of cloudy swelling.

Although the outlook for accomplishing artificial nutrition with anything like exactness by the use of milk seemed most unpromising, it was felt that with milk as the most readily obtainable food, easy of preparation and sterilization, it would be worth giving it a final trial in the hope that some immunity to the poisonous effects might be acquired by using very small amounts at a time and increasing very gradually, waiting for all symptoms to subside before repeating the treatment.

EXPERIMENT 6.—The milk was skimmed and peptonized as in the last experiment, for one and a half hours, then sterilized. A 50 per cent. glucose solution was also prepared, in order to see how this would act in connection with the milk, thus furnishing some extra heat units.

A lively dog was obtained, put on the laboratory fare, weighed daily, and allowed to reach practically a stationary weight, which it did on a diet of 0.61 gram of nitrogen per kilo, although on this diet it put on 0.4 to 0.5 gram of nitrogen. A period of thirteen days was consumed in the experimental feeding, previous to which the dog, as has already been stated, was at an almost constant weight, although the nitrogen balance showed the 0.4 to 0.5 gram plus per day.

The injections were begun with very small amounts, e. g., 0.098 gram of nitrogen per kilo, divided into two injections, and, as a rule, the amount was not increased for forty-eight hours. Including the two days on regular mouth feeding,

preceding the experiment, and on all the thirteen days during which hypodermic nutrition was successfully maintained, the nitrogen balance was determiend daily. While this always showed a minus balance, i. e., the dog was excreting more nitrogen than it received in the food injected, still, with each increase in the amount of food the minus balance grew steadily less until on the tenth and eleventh days it was only 0.5 gram of nitrogen, the body weight remaining almost constant on those days. The food was then reduced and the minus nitrogen balance again increased to —2.62 gram. On increasing the food, it again sank to —0.311 gram on the fourteenth day.

These injections were given precisely as the others, twice daily, twelve hours apart, under aseptic precautions, and the animal showed surprisingly little reaction to them. During the earlier days of the injections, when the amount of nitrogen injected was low and the dog, of course, losing weight, he was not so lively, but was not ill; as the quantity of nitrogen was increased to 0.33 gram per kilo his general well-being improved and he was bright, lively and apparently normal. Up to the point of receiving 0.22 gram of nitrogen per kilo, there was no biuret reaction in the urine, showing that the peptone was being utilized completely. After this, there was always a slight reaction, increasing somewhat as the percentage of nitrogen was increased, although the dog's apparent well-being was improved and he seemed normal.

At times there was a trace of albumin in the urine, but never more; at no time were there casts. The sugar injected varied from nearly 4 grams per kilo per day to a little less than 1 gram, and varying amounts could always be detected in the urine. The lactose from the milk injections alone gave a moderate reduction of the copper, but not a quick, strong reaction, as when the glucose was injected. No accurate estimations of the amount of excreted sugar were made.

The dog's temperature at the beginning of the experiment was 103° F. (somewhat above normal), and never rose over 103.2° F. during the entire period of thirteen days. After the first two days, the dog was never thirsty and refused water during the last eleven days; it received more water by the injections than it really needed.

After the twenty-sixth (the last) injection on the thirteenth day of this experiment, the dog played about, ran to his cage wagging his tail, showing a very nearly normal physical condition, except for the moderate loss in weight, 0.85 kilo. The loss of weight, which set in late in the experiment, probably shows that such a purely artificial form of nutrition can not be maintained indefinitely (Table 3).

SUMMARY.

In offering a short review of these experiments, the results may be stated in a few words as follows:

1. By the ordinary method of rectal alimentation it is practically impossible to nourish patients properly or to maintain nitrogenous equilibrium. There are probably few, if any, exceptions to this rule.

2. The hypodermic use of meat peptones and alkali albuminates is not feasible for artificial nutrition on account of their great toxicity and tendency to cause local necrosis.

3. Skimmed milk, peptonized one and one-half to three hours, may prove fatal if given hypodermically.

4. It was found possible to furnish a dog with full nitrogenous requirements in the form of skimmed milk, peptonized one and one-half hours, and injected hypodermically in gradually increasing doses; when

TABLE 3.

Day.	Weigth in kilos.	Volume of urine in c.c.	Sp. Gr. of urine.	Chemical Examination of urine.			Total urinary N., grams.	Food volume in c.c.	Total food N in gms.	Feces in gms.	Total fecal N in gms.	Nitrogen (gms.) in food per kilo of body weight.	Total nitrogen balance.	Remarks.
				Albumin.	Sugar.	Biuret reaction.								
1.	6.60	230	1012	0	0	0	3.174	Reg.	4.034	39	0.458	0.61	+0.404 N	
2	6.55	255	1014	0	0	0	3.136	Reg.	4.034	25	0.320	0.61	+0.568 N	
3	6.68	145	1043	Trace.	+	0	4.364	135	0.656	0	0.	0.098	—3.708 N	Dog a little depressed.
4	6.50	395	1016	0	+	0	3.179	135	0.656	0	0.	0.1	—2.523 N	Dog better; lively.
5	6.31	220	1024	0	+	0	2.083	135	0.656	7	0.247	0.103	—1.674 N	Dog practically normal.
6	6.35	105+	1051	0	+	0	1.710	150	0.762	*	0.111	0.12	—1.059 N	Some urine contained feces, estimated as "liquid."
7	6.33	190+	1040	Trace.	+	0	2.622	150	0.762	*	0.287	0.12	—2.147 N	Some urine contained feces, estimated as "liquid."
8	6.30	210+	1040	Slight trace.	+	+	2.772	275	1.397	*	0.144	0.221	—1.524 N	Some urine contained feces, estimated as "liquid." First day with + biuret reaction.
9	6.25	255	1033	"	+	+	2.470	275	1.397	0	0.	0.223	—1.073 N	Dog apparently keeps well; not thirsty.
10	6.30	250	1038	"	+	Faint.	2.292	373	2.100	0	0.313	0.333	—0.505 N	Very small minus balance.
11	6.31	260	1038	"	+	"	2.646	373	2.100	0	0.	0.332	—0.546 N	
12	6.10	335	1024	"	+	"	2..401	202	1.139	0	0.	0.186	—2.622 N	Dog continues all right.
13	5.95	240	1033	"	+	"	2.299	205	1.150	6	0.394	0.193	—1.543 N	
14	6.00	215	1049	"	+	"	2.401	373	2.092	0	0.	0.348	—0.311 N	Smallest minus nitrogeous balance.
15	5.75	415+	1033	"	+	"	3.577	373	2.162	0	0.	0.337	—1.640 N	Dog lively and well; trotted back to cage.

* Liquid.

on the larger amounts of food the weight remained almost stationary, the nitrogenous balance showed only 0.3 to 0.5 gram loss, the dog being apparently physically in good condition.

5. For ordinary use, although successfully carried out in this instance, milk peptone when injected hypodermically must be considered dangerous, and until some method for avoiding the greater part of the natural toxicity of the product can be found, should not be used for nutritive purposes in man.

Since nutrition may be thus artificially carried out in dogs, it does not seem improbable that some modification of the method may be found that would be suitable for man, particularly as the minimum human nitrogen requirements are, per kilo, less than one-half that of the dog.

Addenda.—A subsequent attempt was made to nourish a dog on milk to which extract of pancreas had been added at the time of injection in the hope that the process of peptonization would take place slowly in the tissues, thus reducing the tendency to toxic effects from large amounts of peptone. The experiment, however, was a failure, as the material caused wide local necrosis and made the dog exceedingly ill. It was then thought that possibly a dog might be immunized against this form of peptone, that serum from this animal might prove effectual in protecting another. The attempt was made, but, although the dog which it was attempted to immunize showed a lessening reaction to the poisonous effects of the peptone, it never became immune. This, it was found, coincided with the experience of Friedman and Isaacs.[18]

My hearty thanks are due to the attending and house staff of the Presbyterian Hospital for the clinical material and to Prof. Wm. T. Gies, of the Department of Biologic Chemistry of Columbia University at the College of Physicians and Surgeons, for many helpful suggestions and valuable advice in connection with the metabolism experiments as they were carried out under his supervision.

66 W. Fifty-fifth Street.

18. Zeitsch. f. Exp. Thera. Path., 1908.

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